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(54) Title: 7, 9-SUBSTITUTED TETRACYCLINE COMPOUNDS

(57) Abstract: The present invention pertains to novel 7,9-substituted tetracycline compounds. These tetracycline compounds can be used to treat numerous tetracycline compound-responsive states, such as bacterial infections and neoplasms, as well as other known applications for minocycline compounds in general, such as blocking tetracycline efflux and modulation of gene expression.

7, 9-SUBSTITUTED TETRACYCLINE COMPOUNDS

Related Applications

- 5 This application claims priority U.S. Provisional Patent Application Serial No. 60/275,620, entitled "7, 9-Substituted Tetracycline Compounds," filed on March 13, 2001.

Background of the Invention

- 10 The development of the tetracycline antibiotics was the direct result of a systematic screening of soil specimens collected from many parts of the world for evidence of microorganisms capable of producing bacteriocidal and/or bacteriostatic compositions. The first of these novel compounds was introduced in 1948 under the name chlortetracycline. Two years later, oxytetracycline became available. The
15 elucidation of the chemical structure of these compounds confirmed their similarity and furnished the analytical basis for the production of a third member of this group in 1952, tetracycline. A new family of tetracycline compounds, without the ring-attached methyl group present in earlier tetracyclines, was prepared in 1957 and became publicly available in 1967; and minocycline was in use by 1972.

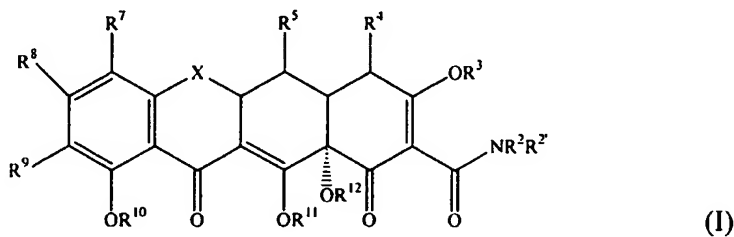
- 20 Recently, research efforts have focused on developing new tetracycline antibiotic compositions effective under varying therapeutic conditions and routes of administration. New tetracycline analogues have also been investigated which may prove to be equal to or more effective than the originally introduced tetracycline compounds. Examples include U.S. Patent Nos. 2,980,584; 2,990,331; 3,062,717;
25 3,165,531; 3,454,697; 3,557,280; 3,674,859; 3,957,980; 4,018,889; 4,024,272; and 4,126,680. These patents are representative of the range of pharmaceutically active tetracycline and tetracycline analogue compositions.

- Historically, soon after their initial development and introduction, the
 tetracyclines were found to be highly effective pharmacologically against rickettsiae; a
30 number of gram-positive and gram-negative bacteria; and the agents responsible for lymphogranuloma venereum, inclusion conjunctivitis, and psittacosis. Hence, tetracyclines became known as "broad spectrum" antibiotics. With the subsequent establishment of their in vitro antimicrobial activity, effectiveness in experimental infections, and pharmacological properties, the tetracyclines as a class rapidly became
35 widely used for therapeutic purposes. However, this widespread use of tetracyclines for both major and minor illnesses and diseases led directly to the emergence of resistance to these antibiotics even among highly susceptible bacterial species both commensal and

pathogenic (e.g., pneumococci and Salmonella). The rise of tetracycline-resistant organisms has resulted in a general decline in use of tetracyclines and tetracycline analogue compositions as antibiotics of choice.

5 Summary of the Invention:

In an embodiment, the invention pertains to 7, 9-substituted tetracycline compounds of Formula I:



10 wherein:

X is $\text{CHC}(\text{R}^{13}\text{Y}'\text{Y})$, CR^6R^6 , S, NR^6 , or O;

R^2 , $\text{R}^{2'}$, $\text{R}^{4'}$, and $\text{R}^{4''}$ are each independently hydrogen, alkyl, alkenyl, alkynyl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, arylalkyl, aryl, heterocyclic, heteroaromatic or a prodrug moiety;

15 R^4 is $\text{NR}^{4'}\text{R}^{4''}$, alkyl, alkenyl, alkynyl, hydroxyl, halogen, or hydrogen;
 $\text{R}^{2'}$, R^3 , R^{10} , R^{11} and R^{12} are each hydrogen or a pro-drug moiety;

R^5 is hydroxyl, hydrogen, thiol, alkanoyl, aroyl, alkaroyl, aryl, heteroaromatic, alkyl, alkenyl, alkynyl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, arylalkyl, alkyl carbonyloxy, or aryl carbonyloxy;

20 R^6 and $\text{R}^{6'}$ are each independently hydrogen, methylene, absent, hydroxyl, halogen, thiol, alkyl, alkenyl, alkynyl, aryl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, or an arylalkyl;

R^7 is nitro, alkyl, alkenyl, alkynyl, aryl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, arylalkyl, amino, arylalkenyl, arylalkynyl, or $-(\text{CH}_2)_{0-3}\text{NR}^{7c}\text{C}(=\text{W}')\text{WR}^{7a}$;

25 R^9 is nitro, alkyl, alkenyl, alkynyl, aryl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, arylalkyl, amino, arylalkenyl, arylalkynyl, thionitroso, or $-(\text{CH}_2)_0$
 ${}_3\text{NR}^{9c}\text{C}(=\text{Z}')\text{ZR}^{9a}$;

Z is $\text{CR}^{9d}\text{R}^{9e}$, S, NR^{9b} or O;

Z' is O, S, or NR^{9f} ;

30 W is $\text{CR}^{7d}\text{R}^{7e}$, S, NR^{7b} or O;

W' is O, NR^{7f} S;

R^{7a} , R^{7b} , R^{7c} , R^{7d} , R^{7e} , R^{9a} , R^{9b} , R^{9c} , R^{9d} , and R^{9e} are each independently hydrogen, acyl, alkyl, alkenyl, alkynyl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, arylalkyl, aryl, heterocyclic, heteroaromatic or a prodrug moiety;

R^8 is hydrogen, hydroxyl, halogen, thiol, alkyl, alkenyl, alkynyl, aryl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, or an arylalkyl;

R^{13} is hydrogen, hydroxy, alkyl, alkenyl, alkynyl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, or an arylalkyl; and

Y' and Y are each independently hydrogen, halogen, hydroxyl, cyano, sulfhydryl, amino, alkyl, alkenyl, alkynyl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, or an arylalkyl, and pharmaceutically acceptable salts thereof.

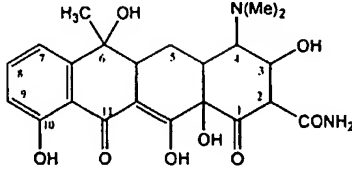
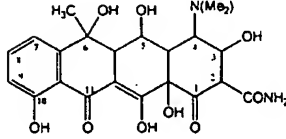
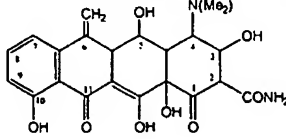
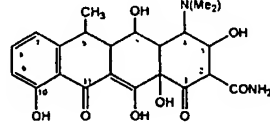
The invention also pertains to a method for treating a tetracycline responsive state in a subject, by administering to the subject a tetracycline compound of the invention (e.g., of Formula I), such that the tetracycline responsive state is treated.

15 Detailed Description of the Invention:

The present invention pertains, at least in part, to novel 7,9- substituted tetracycline compounds. These tetracycline compounds can be used to treat numerous tetracycline compound-responsive states, such as bacterial infections and neoplasms, as well as other known applications for minocycline and tetracycline compounds in general, such as blocking tetracycline efflux and modulation of gene expression.

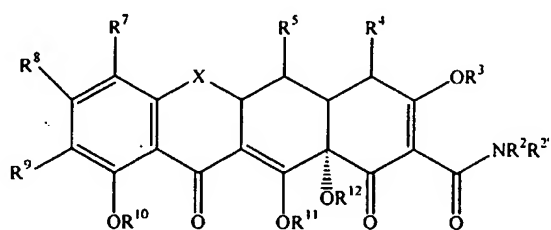
The term "tetracycline compound" includes many compounds with a similar ring structure to tetracycline. Examples of tetracycline compounds include: tetracycline, chlortetracycline, oxytetracycline, demeclocycline, methacycline, sancycline, doxycycline, and minocycline. Other derivatives and analogues comprising a similar four ring structure are also included. Table 1 depicts tetracycline and several known tetracycline derivatives.

TABLE I

 <p>Tetracycline</p>	 <p>Oxytetracycline</p>
 <p>Methacycline</p>	 <p>Doxycycline</p>

The term "7,9-substituted tetracycline compounds" includes tetracycline compounds with substitution at the 7 and 9- positions. In one embodiment, the substitution at the 7- and 9- positions enhances the ability of the tetracycline compound to perform its intended function, e.g., treat tetracycline responsive states. In an embodiment, the 7,9-substituted tetracycline compound is 7,9-substituted tetracycline (e.g., wherein R^4 is $NR^{4'}R^{4''}$; $R^{4'}$ and $R^{4''}$ are methyl, R^5 is hydrogen and X is $CR^6R^{6'}$, wherein R^6 is methyl and $R^{6'}$ is hydroxy); 7,9-substituted doxycycline (e.g., wherein R^4 is $NR^{4'}R^{4''}$; $R^{4'}$ and $R^{4''}$ are methyl, R^5 is hydroxyl and X is $CR^6R^{6'}$, wherein R^6 is methyl and $R^{6'}$ is hydrogen); or 7, 9- substituted sancycline (wherein R^4 is $NR^{4'}R^{4''}$; $R^{4'}$ and $R^{4''}$ are methyl; R^5 is hydrogen and X is $CR^6R^{6'}$ wherein R^6 and $R^{6'}$ are hydrogen atoms. In an embodiment, the substitution at the 7 position of the 7, 9-substituted tetracycline compound is not chlorine or trimethylamino. In one embodiment, R^4 is hydrogen.

The 7, 9-substituted tetracycline compounds of the invention include compounds of Formula I:



(I)

wherein:

- X is $CHC(R^{13}Y'Y)$, CR^6R^6 , S, NR^6 , or O;
- R^2 , R^2' , R^4' , and $R^{4''}$ are each independently hydrogen, alkyl, alkenyl, alkynyl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, arylalkyl, aryl, heterocyclic, heteroaromatic or a prodrug moiety;
- R^4 is $NR^{4'}R^{4''}$, alkyl, alkenyl, alkynyl, hydroxyl, halogen, or hydrogen;
- R^2' , R^3 , R^{10} , R^{11} and R^{12} are each hydrogen or a pro-drug moiety;
- R^5 is hydroxyl, hydrogen, thiol, alkanoyl, aroyl, alkaroyl, aryl, heteroaromatic, alkyl, alkenyl, alkynyl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, arylalkyl, alkyl carbonyloxy, or aryl carbonyloxy;
- R^6 and $R^{6'}$ are each independently hydrogen, methylene, absent, hydroxyl, halogen, thiol, alkyl, alkenyl, alkynyl, aryl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, or an arylalkyl;
- R^7 is nitro, alkyl, alkenyl, alkynyl, aryl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, arylalkyl, amino, arylalkenyl, arylalkynyl, or $-(CH_2)_{0-3}NR^{7c}C(=W')WR^{7a}$;

R^9 is nitro, alkyl, alkenyl, alkynyl, aryl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, arylalkyl, amino, arylalkenyl, arylalkynyl, thionitroso, or $-(CH_2)_0$ - $_3NR^{9c}C(=Z')ZR^{9a}$;

Z is $CR^{9d}R^{9c}$, S, NR^{9b} or O;

5 Z' is O, S, or NR^{9f} ;

W is $CR^{7d}R^{7c}$, S, NR^{7b} or O;

W' is O, NR^{7f} S;

10 R^{7a} , R^{7b} , R^{7c} , R^{7d} , R^{7e} , R^{9a} , R^{9b} , R^{9c} , R^{9d} , and R^{9e} are each independently hydrogen, acyl, alkyl, alkenyl, alkynyl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, arylalkyl, aryl, heterocyclic, heteroaromatic or a prodrug moiety;

R^8 is hydrogen, hydroxyl, halogen, thiol, alkyl, alkenyl, alkynyl, aryl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, or an arylalkyl;

R^{13} is hydrogen, hydroxy, alkyl, alkenyl, alkynyl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, or an arylalkyl; and

15 Y' and Y are each independently hydrogen, halogen, hydroxyl, cyano, sulfhydryl, amino, alkyl, alkenyl, alkynyl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, or an arylalkyl, and pharmaceutically acceptable salts thereof.

The tetracycline compounds of the invention include, for example,
20 compounds wherein X is $CR^6R^{6'}$; R^4 is $NR^{4'}R^{4''}$; R^2 , $R^{2'}$, R^6 , $R^{6'}$, R^8 , R^{10} , R^{11} , and R^{12} are each hydrogen; $R^{4'}$ and $R^{4''}$ are lower alkyl; and R^5 is hydroxy or hydrogen. In an embodiment, $R^{4'}$ and $R^{4''}$ are each methyl and R^5 is hydrogen. The tetracycline compounds of the invention include each possible combination of R^7 and R^9 substituents discussed below.

25 In an embodiment, R^7 is aryl (e.g., heteroaryl or substituted or unsubstituted phenyl). The phenyl R^7 group may be substituted with one or more substituents. Examples of substituents of phenyl R^7 groups include alkyl, alkenyl, halogen, hydroxyl, alkoxy, alkylcarbonyloxy, alkyloxycarbonyl, arylcarbonyloxy, alkoxy-carbonylamino, alkoxy-carbonyloxy, aryloxycarbonyloxy, carboxylate,
30 alkylcarbonyl, alkylaminoacarbonyl, arylalkyl aminocarbonyl, alkenylaminocarbonyl, alkylcarbonyl, arylcarbonyl, aminoalkyl, arylalkylcarbonyl, alkenylcarbonyl, alkoxy-carbonyl, silyl, aminocarbonyl, alkylthiocarbonyl, phosphate, aralkyl, phosphonato, phosphinato, cyano, amino, acylamino, amido, imino, sulfhydryl, alkylthio, sulfate, arylthio, thiocarboxylate, alkylsulfinyl, sulfonato, sulfamoyl,
35 sulfonamido, nitro, cyano, azido, heterocyclyl, alkylaryl, aryl and heteroaryl. In certain embodiments, the substituent is substituted or unsubstituted alkyl (e.g., methyl, ethyl, propyl, butyl, etc.), nitro, halogen (e.g., fluorine, bromine, chlorine,

iodine, etc.), amino (e.g., unsubstituted amino, alkyl amino, dialkylamino (e.g., dimethylamino), or alkoxy (methylenedioxy or methoxy).

R^7 also may be substituted or unsubstituted alkyl (e.g., methyl, ethyl, i-propyl, n-propyl, t-butyl, i-butyl, n-butyl, pentyl, n-pentyl, n-hexyl, or hexyl). The alkyl
5 may be branched or straight chain and may comprise a ring, e.g., a cycloalkyl ring, e.g., cyclohexyl ring.

The alkyl R^7 group may be substituted with any substituent which allows the tetracycline compound to perform its intended function. Examples of substituents include, but are not limited to, alkenyl, halogen (e.g., fluorine, chlorine, bromine,
10 iodine, etc.), hydroxyl, alkoxy (e.g., methoxy, ethoxy, perchloromethoxy, perfluoromethoxy, etc.), alkylcarbonyloxy, alkyloxycarbonyl, arylcarbonyloxy, arylcarbonylamino, alkoxycarbonylamino, alkoxycarbonyloxy, aryloxycarbonyloxy, carboxylate, alkylcarbonyl, alkylaminoacarbonyl, arylalkyl aminocarbonyl, alkenylaminocarbonyl, alkylcarbonyl, arylcarbonyl, aminoalkyl, arylalkylcarbonyl,
15 alkenylcarbonyl, alkoxycarbonyl, silyl, aminocarbonyl, alkylthiocarbonyl, phosphate, aralkyl, phosphonato, phosphinato, cyano, amino, acylamino, amido, imino, sulfhydryl, alkylthio, sulfate, arylthio, thiocarboxylate, alkylsulfinyl, sulfonato, sulfamoyl, sulfonamido, nitro, cyano, azido, heterocyclyl, alkylaryl, aryl and heteroaryl.

Examples of heterocyclic substituents include N-isoindeole-[1,3]-dione
20 (e.g., phthalimide). In an embodiment, the substituent is arylcarbonylamino, e.g., heteroaryl carbonyl amino. The heteroaryl group may be, for example, pyridinyl. Other examples of substituents include amino or carboxylate.

In another embodiment, R^7 is acyl, e.g., acetyl.

In yet another embodiment, R^7 is substituted or unsubstituted alkynyl.

25 Examples of substituents include those which allow the tetracycline compound to perform its intended function. Examples of substituents include, but are not limited to, alkyl (e.g., methyl, ethyl, propyl, butyl, etc.), alkenyl, halogen, hydroxyl, alkoxy, alkylcarbonyloxy, alkyloxycarbonyl, arylcarbonyloxy, arylcarbonylamino, alkoxycarbonylamino, alkoxycarbonyloxy, aryloxycarbonyloxy, carboxylate,
30 alkylcarbonyl, alkylaminoacarbonyl, arylalkyl aminocarbonyl, alkenylaminocarbonyl, alkylcarbonyl, arylcarbonyl, aminoalkyl, arylalkylcarbonyl, alkenylcarbonyl, alkoxycarbonyl, silyl, aminocarbonyl, alkylthiocarbonyl, phosphate, aralkyl, phosphonato, phosphinato, cyano, amino, acylamino, amido, imino, sulfhydryl, alkylthio, sulfate, arylthio, thiocarboxylate, alkylsulfinyl, sulfonato, sulfamoyl,
35 sulfonamido, nitro, cyano, azido, heterocyclyl, alkylaryl, aryl and heteroaryl.

In a further embodiment, the aryl substituent is substituted or unsubstituted phenyl. The phenyl also may be further substituted with one or more

substituents which allow the compound to perform its intended function. Examples of phenyl substituents include, but are not limited to, alkoxy (e.g., methoxy).

The tetracycline compounds of the invention include compounds wherein

5 R^9 is substituted or unsubstituted aryl (e.g., carbocyclic or heteroaryl). In an embodiment, R^9 is substituted or unsubstituted phenyl. The substituted phenyl group can be substituted with any substituent or combination of substituents which allows the compound to perform its intended function. Examples of substituents include, but are not limited to, alkyl, alkenyl, halogen, hydroxyl, alkoxy, alkylcarbonyloxy,

10 alkylloxycarbonyl, arylcarbonyloxy, alkoxycarbonylamino, alkoxycarbonyloxy, aryloxycarbonyloxy, carboxylate, alkylcarbonyl, alkylaminoacarbonyl, arylalkyl aminocarbonyl, alkenylaminocarbonyl, alkylcarbonyl, arylcarbonyl, aminoalkyl, arylalkylcarbonyl, alkenylcarbonyl, alkoxycarbonyl, silyl, aminocarbonyl, alkylthiocarbonyl, phosphate, aralkyl, phosphonato, phosphinato, cyano, amino,

15 acylamino, amido, imino, sulfhydryl, alkylthio, sulfate, arylthio, thiocarboxylate, alkylsulfinyl, sulfonato, sulfamoyl, sulfonamido, nitro, cyano, azido, heterocyclyl, alkylaryl, aryl and heteroaryl.

In a further embodiment, the phenyl R^9 substituent is substituted or unsubstituted alkyl, nitro, halogen, amino, or alkoxy (e.g., methylenedioxy).

20 The invention also includes compounds wherein R^9 is substituted or unsubstituted alkyl (e.g., methyl, ethyl, i-propyl, n-propyl, i-butyl, t-butyl, n-butyl, pentyl, hexyl, etc.). The alkyl group may be substituted with any substituent that allows the compound to perform its intended function. Examples of the substituents include, but are not limited to, alkenyl, halogen, hydroxyl, alkoxy, alkylcarbonyloxy,

25 alkylloxycarbonyl, arylcarbonyloxy, arylcarbonylamino, alkoxycarbonylamino, alkoxycarbonyloxy, aryloxycarbonyloxy, alkylcarbonylamino, carboxylate, alkylcarbonyl, alkylaminoacarbonyl, arylalkyl aminocarbonyl, alkenylaminocarbonyl, alkylcarbonyl, arylcarbonyl, aminoalkyl, arylalkylcarbonyl, alkenylcarbonyl, alkoxycarbonyl, silyl, aminocarbonyl, alkylthiocarbonyl, phosphate, aralkyl,

30 phosphonato, phosphinato, cyano, amino, acylamino, amido, imino, sulfhydryl, alkylthio, sulfate, arylthio, thiocarboxylate, alkylsulfinyl, sulfonato, sulfamoyl, sulfonamido, nitro, cyano, azido, heterocyclyl, alkylaryl, aryl and heteroaryl.

In an embodiment, wherein said substituent is unsubstituted amino. In a further embodiment, the R^9 group is aminomethyl. In another, the alkyl R^9 group is

35 substituted with arylcarbonylamino (e.g., heteroarylcarbonylamino, e.g., pyridinylcarbonylamino) or alkylcarbonylamino.

In another further embodiment, the R⁹ alkyl group is substituted with a heterocyclic substituent, such as isoindole-[1,3]-dione (e.g., phthalimide).

In an embodiment, R⁷ is acyl, e.g., acetyl.

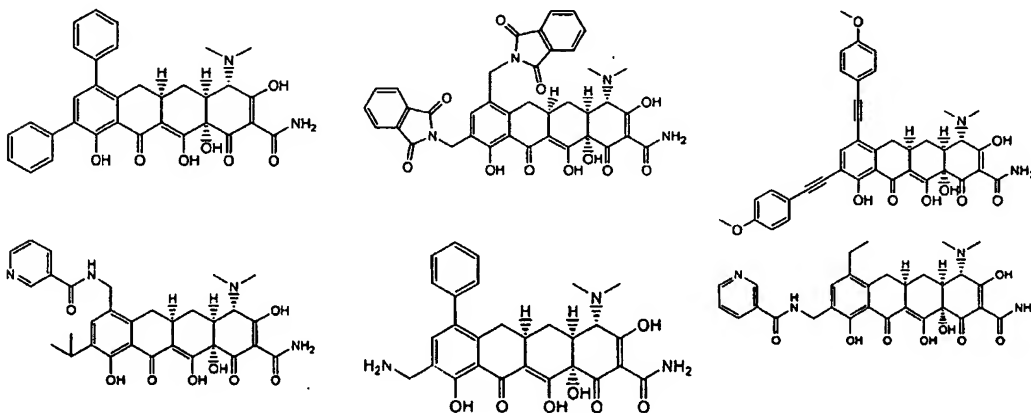
In yet another embodiment, R⁹ is substituted or unsubstituted alkynyl.

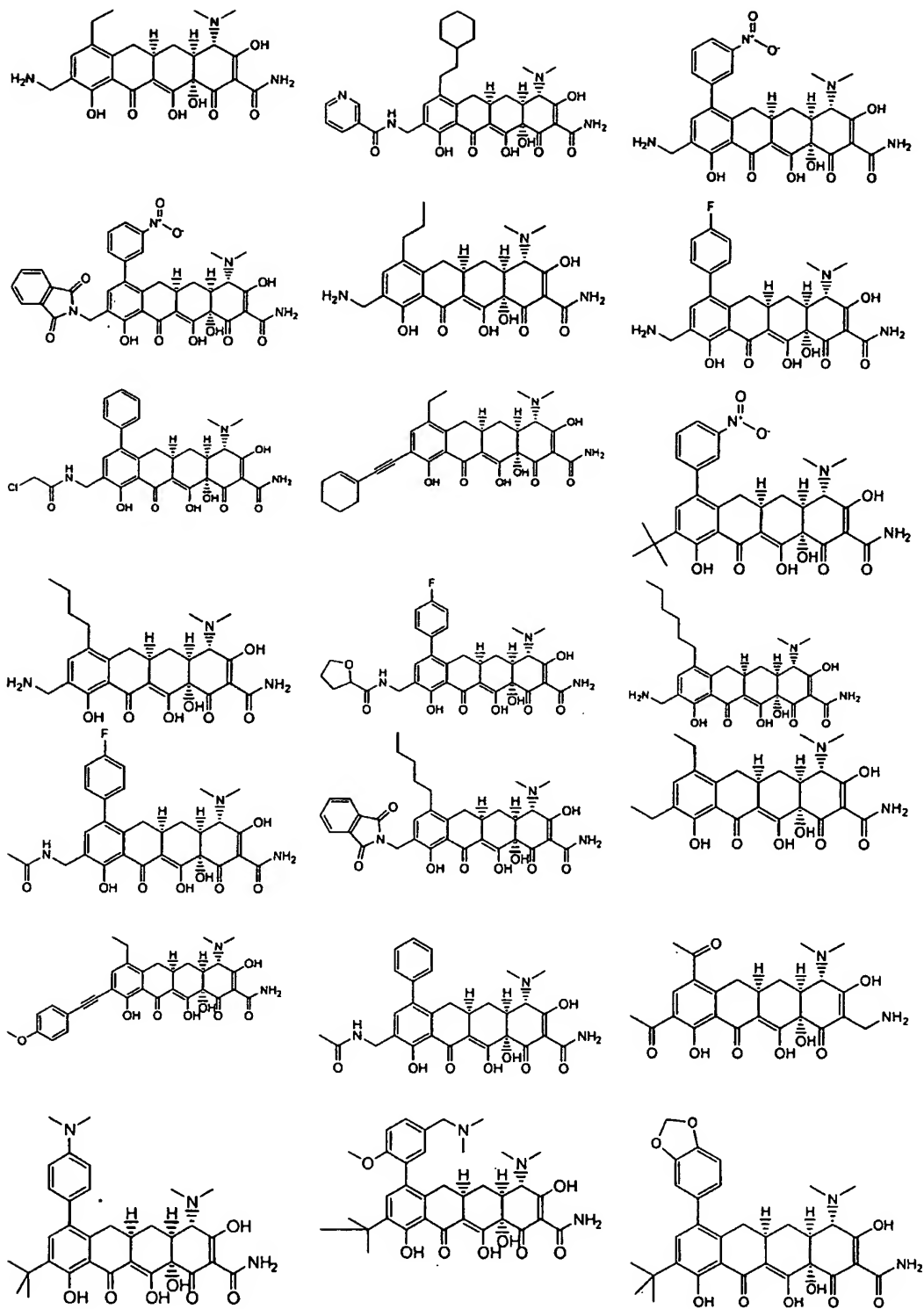
- 5 The alkynyl R⁹ group can be substituted with any substituent which allows the tetracycline compound of the invention to perform its intended function. Examples of substituents include, but are not limited to, alkyl (e.g., methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, etc.), alkenyl, halogen, hydroxyl, alkoxy, alkylcarbonyloxy, alkyloxycarbonyl, arylcarbonyloxy, arylcarbonylamino, alkoxy carbonylamino, alkoxy carbonyloxy, aryloxycarbonyloxy, carboxylate, alkylcarbonyl, alkylaminoacarbonyl, arylalkyl aminocarbonyl, alkenylaminocarbonyl, alkylcarbonyl, arylcarbonyl, aminoalkyl, arylalkylcarbonyl, alkenylcarbonyl, alkoxy carbonyl, silyl, aminocarbonyl, alkylthiocarbonyl, phosphate, aralkyl, phosphonato, phosphinato, cyano, amino, acylamino, amido, imino, sulfhydryl, alkylthio, sulfate, arylthio, thiocarboxylate, alkylsulfinyl, sulfonato, sulfamoyl, sulfonamido, nitro, cyano, azido, heterocyclyl, alkylaryl, aryl and heteroaryl.

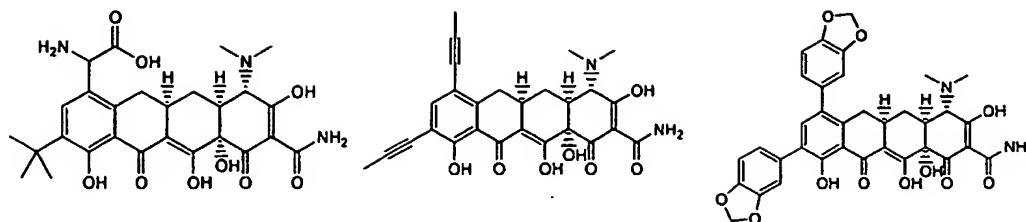
- 20 In a further embodiment, the aryl substituted alkynyl R⁹ moiety is, for example, substituted or unsubstituted phenyl. The phenyl may be substituted with, for example, alkoxy, e.g., methoxy. Examples of alkenyl substituents include cycloalkenes such as, cyclohexene.

In one embodiment, R⁹ is not unsubstituted phenyl when R⁷ is unsubstituted phenyl.

- 25 Examples of 7,9-substituted tetracycline compounds of the invention include those listed below and in Table 2:



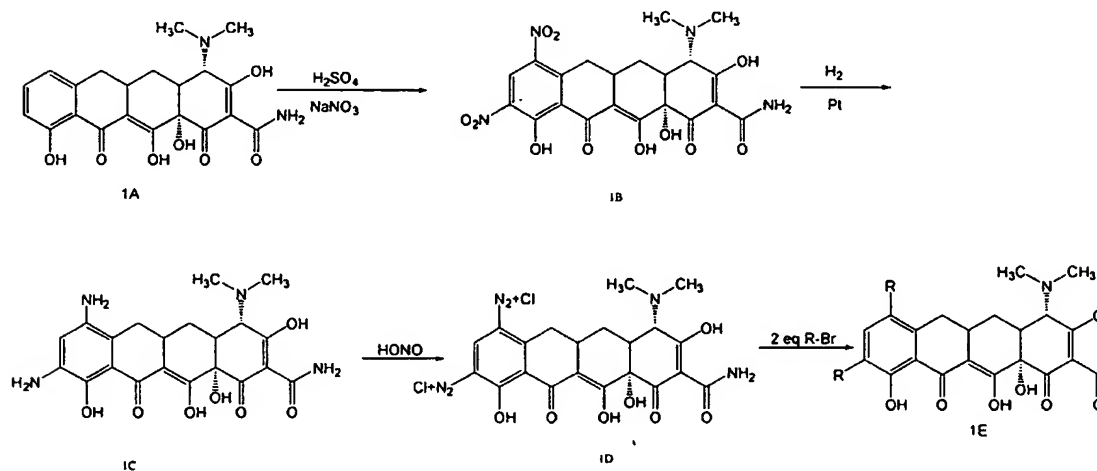




The invention also pertains to each of the 7,9-substituted tetracycline compounds shown in Table 2, as well as their pharmaceutically acceptable salts.

The 7,9-disubstituted tetracycline compounds of this invention can be synthesized using the methods described in Schemes 1-5.

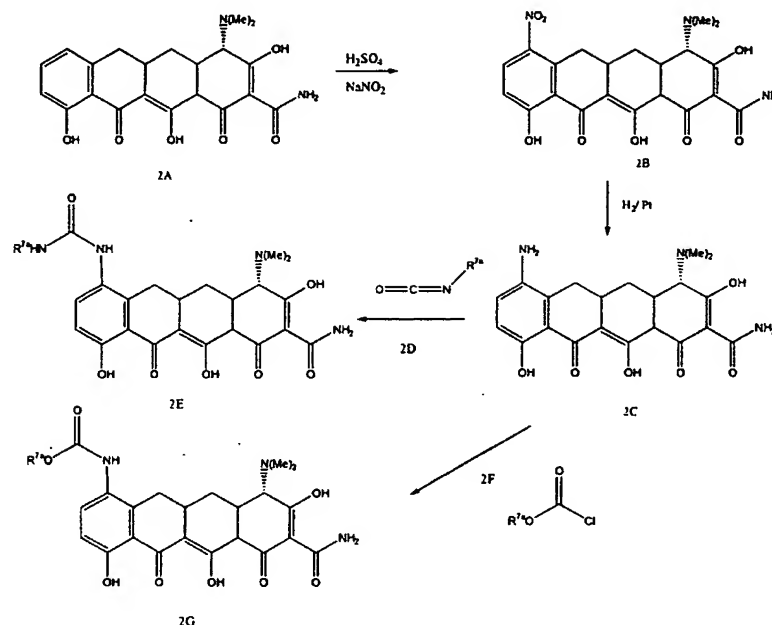
Certain 7,9-substituted tetracycline compounds can be synthesized by the method shown in Scheme 1. Although in each scheme sancycline is used as the tetracycline compound, one of skill in the art will appreciate that the methodology can also be applied to other tetracycline compounds such as tetracycline and doxycycline. Furthermore, some of the following methods are shown for seven substituted compounds. Similar protocols can be followed to substituted the compounds at the 9 position.



SCHEME 1

Generally, 7,9-substituted tetracycline compounds can be synthesized as shown in Scheme 1 for sancycline. Sancycline (1A) is treated with sulfuric acid and sodium nitrate. The resulting product is 7,9-nitro (1B) sancycline. The nitro sancycline compound is then treated with hydrogen gas and a platinum catalyst to yield the 7,9-amino sancycline compound, 1C. To synthesize derivatives, the 7,9-amino sancycline compound is treated with HONO, to yield the diazonium salt (1D). The salt can subsequently be treated with numerous compounds possessing an alkene or n bond

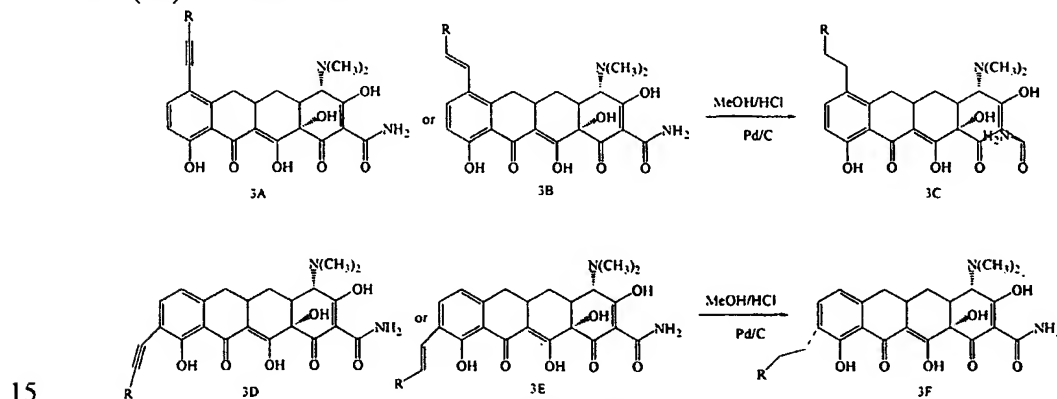
functional group such as alkenes, aryls, and alkynyls (e.g., RBr) yielding the 7,9-substituted sancycline compound (1E).



5

SCHEME 2

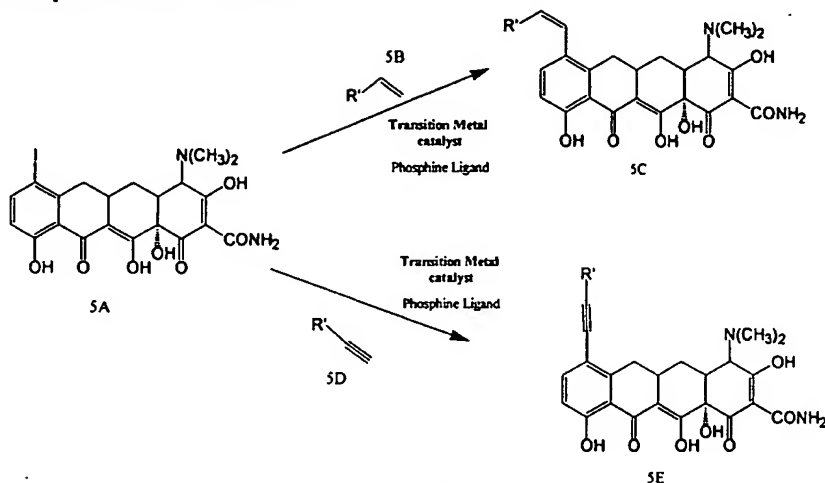
As shown in Scheme 2, tetracycline compounds of the invention wherein R^7 is a carbamate or a urea derivative can be synthesized using the following protocol. Sancycline (2A) is treated with NaNO_2 under acidic conditions forming 7-nitrosancycline (2B) in a mixture of 9-positional isomers. 7-nitrosancycline (2B) is then treated with H_2 gas and a platinum catalyst to form the 7-amino sancycline derivative (2C). To form the urea derivative (2E), isocyanate (2D) is reacted with the 7-amino sancycline derivative (2C). To form the carbamate (2G), the appropriate acid chloride ester (2F) is reacted with 2C.



15

SCHEME 3

with an additional copper salt, e.g., CuI. The resulting compound can then be purified using techniques known in the art.



SCHEME 5

5 The compounds of the invention can also be synthesized using Heck-type cross coupling reactions. As shown in Scheme 5, Heck-type cross-couplings can be performed using a halogenated tetracycline compound (e.g., 7-iodosancycline, 5A), a reactive alkene (5B) or alkyne (5D), and an appropriate palladium or other transition metal catalyst. The resulting 7-substituted alkenyl (5C) or 7-substituted alkynyl (5E)
10 tetracycline compound can then be purified using techniques known in the art.

Other substituted tetracycline compounds of the invention can be synthesized by using one or more of the following synthetic methods at either the 7- or 9- position, followed by the same or different chemistry at the other position. For example, if a group was placed at the 7-position, any of the above reaction methods
15 could be used to further derivatize the 9- position, as shown in Example 1.

The term "alkyl" includes saturated aliphatic groups, including straight-chain alkyl groups (e.g., methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, nonyl, decyl, etc.), branched-chain alkyl groups (isopropyl, tert-butyl, isobutyl, etc.), cycloalkyl (alicyclic) groups (cyclopropyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl), alkyl
20 substituted cycloalkyl groups, and cycloalkyl substituted alkyl groups. The term alkyl further includes alkyl groups, which can further include oxygen, nitrogen, sulfur or phosphorous atoms replacing one or more carbons of the hydrocarbon backbone. In certain embodiments, a straight chain or branched chain alkyl has 6 or fewer carbon atoms in its backbone (e.g., C₁-C₆ for straight chain, C₃-C₆ for branched chain), and
25 more preferably 4 or fewer. Likewise, preferred cycloalkyls have from 3-8 carbon

atoms in their ring structure, and more preferably have 5 or 6 carbons in the ring structure. The term C₁-C₆ includes alkyl groups containing 1 to 6 carbon atoms.

Moreover, the term alkyl includes both "unsubstituted alkyls" and "substituted alkyls", the latter of which refers to alkyl moieties having substituents replacing a hydrogen on one or more carbons of the hydrocarbon backbone. Such substituents can include, for example, alkenyl, alkynyl, halogen, hydroxyl, alkylcarbonyloxy, arylcarbonyloxy, alkoxycarbonyloxy, aryloxy carbonyloxy, carboxylate, alkylcarbonyl, arylcarbonyl, alkoxycarbonyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, alkylthiocarbonyl, alkoxyl, phosphate, phosphonate, phosphinato, cyano, amino (including alkyl amino, dialkylamino, arylamino, diarylamino, and alkylarylamino), acylamino (including alkylcarbonylamino, arylcarbonylamino, carbamoyl and ureido), amidino, imino, sulfhydryl, alkylthio, arylthio, thiocarboxylate, sulfates, alkylsulfinyl, sulfonate, sulfamoyl, sulfonamido, nitro, trifluoromethyl, cyano, azido, heterocyclyl, alkylaryl, or an aromatic or heteroaromatic moiety. Cycloalkyls can be further substituted, e.g., with the substituents described above. An "alkylaryl" or an "arylalkyl" moiety is an alkyl substituted with an aryl (e.g., phenylmethyl (benzyl)). The term "alkyl" also includes the side chains of natural and unnatural amino acids.

The term "aryl" includes groups, including 5- and 6-membered single-ring aromatic groups that may include from zero to four heteroatoms, for example, benzene, phenyl, pyrrole, furan, thiophene, thiazole, isothiazole, imidazole, triazole, tetrazole, pyrazole, oxazole, isooxazole, pyridine, pyrazine, pyridazine, and pyrimidine, and the like. Furthermore, the term "aryl" includes multicyclic aryl groups, e.g., tricyclic, bicyclic, e.g., naphthalene, benzoxazole, benzodioxazole, benzothiazole, benzoimidazole, benzothiophene, methylenedioxyphenyl, quinoline, isoquinoline, naphthridine, indole, benzofuran, purine, benzofuran, deazapurine, or indolizine. Those aryl groups having heteroatoms in the ring structure may also be referred to as "aryl heterocycles", "heterocycles," "heteroaryls" or "heteroaromatics". The aromatic ring can be substituted at one or more ring positions with such substituents as described above, as for example, halogen, hydroxyl, alkoxy, alkylcarbonyloxy, arylcarbonyloxy, alkoxycarbonyloxy, aryloxy carbonyloxy, carboxylate, alkylcarbonyl, alkylaminoacarbonyl, arylalkyl aminocarbonyl, alkenylaminocarbonyl, alkylcarbonyl, arylcarbonyl, arylalkylcarbonyl, alkenylcarbonyl, alkoxycarbonyl, aminocarbonyl, alkylthiocarbonyl, phosphate, phosphonate, phosphinato, cyano, amino (including alkyl amino, dialkylamino, arylamino, diarylamino, and alkylarylamino), acylamino (including alkylcarbonylamino, arylcarbonylamino, carbamoyl and ureido), amidino, imino, sulfhydryl, alkylthio, arylthio, thiocarboxylate, sulfates, alkylsulfinyl, sulfonate,

sulfamoyl, sulfonamido, nitro, trifluoromethyl, cyano, azido, heterocyclyl, alkylaryl, or an aromatic or heteroaromatic moiety. Aryl groups can also be fused or bridged with alicyclic or heterocyclic rings which are not aromatic so as to form a polycycle (e.g., tetralin).

5 The term "alkenyl" includes unsaturated aliphatic groups analogous in length and possible substitution to the alkyls described above, but that contain at least one double bond.

 For example, the term "alkenyl" includes straight-chain alkenyl groups (e.g., ethylenyl, propenyl, butenyl, pentenyl, hexenyl, heptenyl, octenyl, nonenyl, 10 decenyl, etc.), branched-chain alkenyl groups, cycloalkenyl (alicyclic) groups (cyclopropenyl, cyclopentenyl, cyclohexenyl, cycloheptenyl, cyclooctenyl), alkyl or alkenyl substituted cycloalkenyl groups, and cycloalkyl or cycloalkenyl substituted alkenyl groups. The term alkenyl further includes alkenyl groups which include oxygen, nitrogen, sulfur or phosphorous atoms replacing one or more carbons of the hydrocarbon 15 backbone. In certain embodiments, a straight chain or branched chain alkenyl group has 6 or fewer carbon atoms in its backbone (e.g., C₂-C₆ for straight chain, C₃-C₆ for branched chain). Likewise, cycloalkenyl groups may have from 3-8 carbon atoms in their ring structure, and more preferably have 5 or 6 carbons in the ring structure. The term C₂-C₆ includes alkenyl groups containing 2 to 6 carbon atoms.

20 Moreover, the term alkenyl includes both "unsubstituted alkenyls" and "substituted alkenyls", the latter of which refers to alkenyl moieties having substituents replacing a hydrogen on one or more carbons of the hydrocarbon backbone. Such substituents can include, for example, alkyl groups, alkynyl groups, halogens, hydroxyl, alkylcarbonyloxy, arylcarbonyloxy, alkoxycarbonyloxy, aryloxy carbonyloxy, 25 carboxylate, alkylcarbonyl, arylcarbonyl, alkoxycarbonyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, alkylthiocarbonyl, alkoxyl, phosphate, phosphonato, phosphinato, cyano, amino (including alkyl amino, dialkylamino, arylamino, diarylamino, and alkylarylamino), acylamino (including alkylcarbonylamino, arylcarbonylamino, carbamoyl and ureido), amidino, imino, sulfhydryl, alkylthio, 30 arylthio, thiocarboxylate, sulfates, alkylsulfinyl, sulfonato, sulfamoyl, sulfonamido, nitro, trifluoromethyl, cyano, azido, heterocyclyl, alkylaryl, or an aromatic or heteroaromatic moiety.

 The term "alkynyl" includes unsaturated aliphatic groups analogous in length and possible substitution to the alkyls described above, but which contain at least 35 one triple bond.

 For example, the term "alkynyl" includes straight-chain alkynyl groups (e.g., ethynyl, propynyl, butynyl, pentynyl, hexynyl, heptynyl, octynyl, nonynyl,

decynyl, etc.), branched-chain alkynyl groups, and cycloalkyl or cycloalkenyl substituted alkynyl groups. The term alkynyl further includes alkynyl groups which include oxygen, nitrogen, sulfur or phosphorous atoms replacing one or more carbons of the hydrocarbon backbone. In certain embodiments, a straight chain or branched chain
 5 alkynyl group has 6 or fewer carbon atoms in its backbone (e.g., C₂-C₆ for straight chain, C₃-C₆ for branched chain). The term C₂-C₆ includes alkynyl groups containing 2 to 6 carbon atoms.

Moreover, the term alkynyl includes both "unsubstituted alkynyls" and "substituted alkynyls", the latter of which refers to alkynyl moieties having substituents replacing a hydrogen on one or more carbons of the hydrocarbon backbone. Such
 10 substituents can include, for example, alkyl groups, alkynyl groups, halogens, hydroxyl, alkylcarbonyloxy, arylcarbonyloxy, alkoxycarbonyloxy, aryloxy carbonyloxy, carboxylate, alkylcarbonyl, arylcarbonyl, alkoxycarbonyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, alkylthiocarbonyl, alkoxyl, phosphate,
 15 phosphonato, phosphinato, cyano, amino (including alkyl amino, dialkylamino, arylamino, diarylamino, and alkylarylamino), acylamino (including alkylcarbonylamino, arylcarbonylamino, carbamoyl and ureido), amidino, imino, sulfhydryl, alkylthio, arylthio, thiocarboxylate, sulfates, alkylsulfinyl, sulfonato, sulfamoyl, sulfonamido, nitro, trifluoromethyl, cyano, azido, heterocyclyl, alkylaryl, or an aromatic or
 20 heteroaromatic moiety.

Unless the number of carbons is otherwise specified, "lower alkyl" as used herein means an alkyl group, as defined above, but having from one to five carbon atoms in its backbone structure. "Lower alkenyl" and "lower alkynyl" have chain lengths of, for example, 2-5 carbon atoms.

The term "acyl" includes compounds and moieties which contain the acyl
 25 radical (CH₃CO-) or a carbonyl group. It includes substituted acyl moieties. The term "substituted acyl" includes acyl groups where one or more of the hydrogen atoms are replaced by for example, alkyl groups, alkynyl groups, halogens, hydroxyl, alkylcarbonyloxy, arylcarbonyloxy, alkoxycarbonyloxy, aryloxy carbonyloxy,
 30 carboxylate, alkylcarbonyl, arylcarbonyl, alkoxycarbonyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, alkylthiocarbonyl, alkoxyl, phosphate, phosphonato, phosphinato, cyano, amino (including alkyl amino, dialkylamino, arylamino, diarylamino, and alkylarylamino), acylamino (including alkylcarbonylamino, arylcarbonylamino, carbamoyl and ureido), amidino, imino, sulfhydryl, alkylthio,
 35 arylthio, thiocarboxylate, sulfates, alkylsulfinyl, sulfonato, sulfamoyl, sulfonamido, nitro, trifluoromethyl, cyano, azido, heterocyclyl, alkylaryl, or an aromatic or heteroaromatic moiety.

The term "acylamino" includes moieties wherein an acyl moiety is bonded to an amino group. For example, the term includes alkylcarbonylamino, arylcarbonylamino, carbamoyl and ureido groups.

5 The term "aroyl" includes compounds and moieties with an aryl or heteroaromatic moiety bound to a carbonyl group. Examples of aroyl groups include phenylcarboxy, naphthyl carboxy, etc.

The terms "alkoxyalkyl", "alkylaminoalkyl" and "thioalkoxyalkyl" include alkyl groups, as described above, which further include oxygen, nitrogen or sulfur atoms replacing one or more carbons of the hydrocarbon backbone, e.g., oxygen,
10 nitrogen or sulfur atoms.

The term "alkoxy" includes substituted and unsubstituted alkyl, alkenyl, and alkynyl groups covalently linked to an oxygen atom. Examples of alkoxy groups include methoxy, ethoxy, isopropoxy, propoxy, butoxy, and pentoxy groups. Examples of substituted alkoxy groups include halogenated alkoxy groups. The alkoxy
15 groups can be substituted with groups such as alkenyl, alkynyl, halogen, hydroxyl, alkylcarbonyloxy, arylcarbonyloxy, alkoxycarbonyloxy, aryloxycarbonyloxy, carboxylate, alkylcarbonyl, arylcarbonyl, alkoxycarbonyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, alkylthiocarbonyl, alkoxyl, phosphate, phosphonato, phosphinato, cyano, amino (including alkyl amino, dialkylamino,
20 arylamino, diarylamino, and alkylarylamino), acylamino (including alkylcarbonylamino, arylcarbonylamino, carbamoyl and ureido), amidino, imino, sulfhydryl, alkylthio, arylthio, thiocarboxylate, sulfates, alkylsulfanyl, sulfonato, sulfamoyl, sulfonamido, nitro, trifluoromethyl, cyano, azido, heterocyclyl, alkylaryl, or an aromatic or heteroaromatic moieties. Examples of halogen substituted alkoxy groups include, but
25 are not limited to, fluoromethoxy, difluoromethoxy, trifluoromethoxy, chloromethoxy, dichloromethoxy, trichloromethoxy, etc.

The term "amine" or "amino" includes compounds where a nitrogen atom is covalently bonded to at least one carbon or heteroatom. The term "alkyl amino" includes groups and compounds wherein the nitrogen is bound to at least one additional
30 alkyl group. The term "dialkyl amino" includes groups wherein the nitrogen atom is bound to at least two additional alkyl groups. The term "arylamino" and "diarylamino" include groups wherein the nitrogen is bound to at least one or two aryl groups, respectively. The term "alkylarylamino," "alkylaminoaryl" or "arylaminoalkyl" refers to an amino group which is bound to at least one alkyl group and at least one aryl group.
35 The term "alkaminoalkyl" refers to an alkyl, alkenyl, or alkynyl group bound to a nitrogen atom which is also bound to an alkyl group.

The term "amide" or "aminocarbonyl" includes compounds or moieties which contain a nitrogen atom which is bound to the carbon of a carbonyl or a thiocarbonyl group. The term includes "alkaminocarbonyl" or "alkylaminocarbonyl" groups which include alkyl, alkenyl, aryl or alkynyl groups bound to an amino group
5 bound to a carbonyl group. It includes arylaminocarbonyl groups which include aryl or heteroaryl moieties bound to an amino group which is bound to the carbon of a carbonyl or thiocarbonyl group. The terms "alkylaminocarbonyl," "alkenylaminocarbonyl," "alkynylaminocarbonyl," "arylaminocarbonyl," "alkylcarbonylamino," "alkenylcarbonylamino," "alkynylcarbonylamino," and "arylcarbonylamino" are
10 included in term "amide." Amides also include urea groups (aminocarbonylamino) and carbamates (oxycarbonylamino).

The term "carbonyl" or "carboxy" includes compounds and moieties which contain a carbon connected with a double bond to an oxygen atom. The carbonyl can be further substituted with any moiety which allows the compounds of the invention
15 to perform its intended function. For example, carbonyl moieties may be substituted with alkyls, alkenyls, alkynyls, aryls, alkoxy, aminos, etc. Examples of moieties which contain a carbonyl include aldehydes, ketones, carboxylic acids, amides, esters, anhydrides, etc.

The term "thiocarbonyl" or "thiocarboxy" includes compounds and
20 moieties which contain a carbon connected with a double bond to a sulfur atom.

The term "ether" includes compounds or moieties which contain an oxygen bonded to two different carbon atoms or heteroatoms. For example, the term includes "alkoxyalkyl" which refers to an alkyl, alkenyl, or alkynyl group covalently
25 bonded to an oxygen atom which is covalently bonded to another alkyl group.

The term "ester" includes compounds and moieties which contain a carbon or a heteroatom bound to an oxygen atom which is bonded to the carbon of a carbonyl group. The term "ester" includes alkoxycarboxy groups such as methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, butoxycarbonyl, pentoxycarbonyl,
etc. The alkyl, alkenyl, or alkynyl groups are as defined above.

The term "thioether" includes compounds and moieties which contain a sulfur atom bonded to two different carbon or hetero atoms. Examples of thioethers include, but are not limited to alkthioalkyls, alkthioalkenyls, and alkthioalkynyls. The term "alkthioalkyls" include compounds with an alkyl, alkenyl, or alkynyl group bonded
30 to a sulfur atom which is bonded to an alkyl group. Similarly, the term "alkthioalkenyls" and alkthioalkynyls" refer to compounds or moieties wherein an alkyl, alkenyl, or alkynyl group is bonded to a sulfur atom which is covalently bonded to an alkynyl group.

The term "hydroxy" or "hydroxyl" includes groups with an -OH or -O[•].

The term "halogen" includes fluorine, bromine, chlorine, iodine, etc. The term "perhalogenated" generally refers to a moiety wherein all hydrogens are replaced by halogen atoms.

5 The terms "polycyclyl" or "polycyclic radical" refer to two or more cyclic rings (e.g., cycloalkyls, cycloalkenyls, cycloalkynyls, aryls and/or heterocyclyls) in which two or more carbons are common to two adjoining rings, e.g., the rings are "fused rings". Rings that are joined through non-adjacent atoms are termed "bridged" rings. Each of the rings of the polycycle can be substituted with such substituents as described
10 above, as for example, halogen, hydroxyl, alkylcarbonyloxy, arylcarbonyloxy, alkoxycarbonyloxy, aryloxy carbonyloxy, carboxylate, alkylcarbonyl, alkoxycarbonyl, alkylaminoacarbonyl, arylalkylaminocarbonyl, alkenylaminocarbonyl, alkylcarbonyl, arylcarbonyl, arylalkyl carbonyl, alkenylcarbonyl, aminocarbonyl, alkylthiocarbonyl, alkoxy, phosphate, phosphonato, phosphinato, cyano, amino (including alkyl amino,
15 dialkylamino, arylamino, diarylamino, and alkylarylamino), acylamino (including alkylcarbonylamino, arylcarbonylamino, carbamoyl and ureido), amidino, imino, sulfhydryl, alkylthio, arylthio, thiocarboxylate, sulfates, alkylsulfinyl, sulfonato, sulfamoyl, sulfonamido, nitro, trifluoromethyl, cyano, azido, heterocyclyl, alkyl, alkylaryl, or an aromatic or heteroaromatic moiety.

20 The term "heteroatom" includes atoms of any element other than carbon or hydrogen. Preferred heteroatoms are nitrogen, oxygen, sulfur and phosphorus.

 The term "prodrug moiety" includes moieties which can be metabolized *in vivo* to a hydroxyl group and moieties which may advantageously remain esterified *in vivo*. Preferably, the prodrugs moieties are metabolized *in vivo* by esterases or by other
25 mechanisms to hydroxyl groups or other advantageous groups. Examples of prodrugs and their uses are well known in the art (See, e.g., Berge et al. (1977) "Pharmaceutical Salts", *J. Pharm. Sci.* 66:1-19). The prodrugs can be prepared *in situ* during the final isolation and purification of the compounds, or by separately reacting the purified compound in its free acid form or hydroxyl with a suitable esterifying agent. Hydroxyl
30 groups can be converted into esters *via* treatment with a carboxylic acid. Examples of prodrug moieties include substituted and unsubstituted, branch or unbranched lower alkyl ester moieties, (e.g., propionic acid esters), lower alkenyl esters, di-lower alkyl-amino lower-alkyl esters (e.g., dimethylaminoethyl ester), acylamino lower alkyl esters (e.g., acetyloxymethyl ester), acyloxy lower alkyl esters (e.g., pivaloyloxymethyl ester),
35 aryl esters (phenyl ester), aryl-lower alkyl esters (e.g., benzyl ester), substituted (e.g., with methyl, halo, or methoxy substituents) aryl and aryl-lower alkyl esters, amides,

lower-alkyl amides, di-lower alkyl amides, and hydroxy amides. Preferred prodrug moieties are propionic acid esters and acyl esters.

It will be noted that the structure of some of the tetracycline compounds of this invention includes asymmetric carbon atoms. It is to be understood accordingly that the isomers arising from such asymmetry (e.g., all enantiomers and diastereomers) are included within the scope of this invention, unless indicated otherwise. Such isomers can be obtained in substantially pure form by classical separation techniques and by stereochemically controlled synthesis. Furthermore, the structures and other compounds and moieties discussed in this application also include all tautomers thereof.

10

The invention also pertains to methods for treating a tetracycline responsive states in subjects, by administering to a subject an effective amount of a 7-substituted tetracycline compound of the invention (e.g., a compound of Formula (I) or shown in Table 1), such that the tetracycline responsive state is treated.

15

The language "tetracycline compound responsive state" includes states which can be treated, prevented, or otherwise ameliorated by the administration of a tetracycline compound of the invention. Tetracycline compound responsive states include bacterial infections (including those which are resistant to other tetracycline compounds), cancer, diabetes, and other states for which tetracycline compounds have been found to be active (see, for example, U.S. Patent Nos. 5,789,395; 5,834,450; and 5,532,227). Compounds of the invention can be used to prevent or control important mammalian and veterinary diseases such as diarrhea, urinary tract infections, infections of skin and skin structure, ear, nose and throat infections, wound infection, mastitis and the like. In addition, methods for treating neoplasms using tetracycline compounds of the invention are also included (van der Bozert et al., *Cancer Res.*, 48:6686-6690 (1988)).

Bacterial infections may be caused by a wide variety of gram positive and gram negative bacteria. The compounds of the invention are useful as antibiotics against organisms which are resistant to other tetracycline compounds. The antibiotic activity of the tetracycline compounds of the invention may be determined using the method discussed in Example 2, or by using the in vitro standard broth dilution method described in Waitz, J.A., *National Commission for Clinical Laboratory Standards, Document M7-A2*, vol. 10, no. 8, pp. 13-20, 2nd edition, Villanova, PA (1990).

The tetracycline compounds may also be used to treat infections traditionally treated with tetracycline compounds such as, for example, rickettsiae; a number of gram-positive and gram-negative bacteria; and the agents responsible for lymphogranuloma venereum, inclusion conjunctivitis, psittacosis. The tetracycline

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compounds may be used to treat infections of, e.g., *K. pneumoniae*, *Salmonella*, *E. hirae*, *A. baumannii*, *B. catarrhalis*, *H. influenzae*, *P. aeruginosa*, *E. faecium*, *E. coli*, *S. aureus* or *E. faecalis*. In one embodiment, the tetracycline compound is used to treat a bacterial infection that is resistant to other tetracycline antibiotic compounds. The
5 tetracycline compound of the invention may be administered with a pharmaceutically acceptable carrier.

The language "effective amount" of the compound is that amount necessary or sufficient to treat or prevent a tetracycline compound responsive state. The effective amount can vary depending on such factors as the size and weight of the
10 subject, the type of illness, or the particular tetracycline compound. For example, the choice of the tetracycline compound can affect what constitutes an "effective amount". One of ordinary skill in the art would be able to study the aforementioned factors and make the determination regarding the effective amount of the tetracycline compound without undue experimentation.

15 The invention also pertains to methods of treatment against microorganism infections and associated diseases. The methods include administration of an effective amount of one or more tetracycline compounds to a subject. The subject can be either a plant or, advantageously, an animal, e.g., a mammal, e.g., a human.

In the therapeutic methods of the invention, one or more tetracycline
20 compounds of the invention may be administered alone to a subject, or more typically a compound of the invention will be administered as part of a pharmaceutical composition in mixture with conventional excipient, i.e., pharmaceutically acceptable organic or inorganic carrier substances suitable for parenteral, oral or other desired administration and which do not deleteriously react with the active compounds and are not deleterious
25 to the recipient thereof.

The invention also pertains to pharmaceutical compositions comprising a therapeutically effective amount of a tetracycline compound (e.g., a compound of Formula 1, Table 2, or other compound described herein) and, optionally, a pharmaceutically acceptable carrier.

30 The language "pharmaceutically acceptable carrier" includes substances capable of being coadministered with the tetracycline compound(s), and which allow both to perform their intended function, e.g., treat or prevent a tetracycline responsive state. Suitable pharmaceutically acceptable carriers include but are not limited to water, salt solutions, alcohol, vegetable oils, polyethylene glycols, gelatin, lactose, amylose,
35 magnesium stearate, talc, silicic acid, viscous paraffin, perfume oil, fatty acid monoglycerides and diglycerides, petroethral fatty acid esters, hydroxymethyl-cellulose, polyvinylpyrrolidone, etc. The pharmaceutical preparations can be sterilized and if

desired mixed with auxiliary agents, e.g., lubricants, preservatives, stabilizers, wetting agents, emulsifiers, salts for influencing osmotic pressure, buffers, colorings, flavorings and/or aromatic substances and the like which do not deleteriously react with the active compounds of the invention.

5 The tetracycline compounds of the invention that are basic in nature are capable of forming a wide variety of salts with various inorganic and organic acids. The acids that may be used to prepare pharmaceutically acceptable acid addition salts of the tetracycline compounds of the invention that are basic in nature are those that form non-toxic acid addition salts, i.e., salts containing pharmaceutically acceptable anions, such
10 as the hydrochloride, hydrobromide, hydroiodide, nitrate, sulfate, bisulfate, phosphate, acid phosphate, isonicotinate, acetate, lactate, salicylate, citrate, acid citrate, tartrate, pantothenate, bitartrate, ascorbate, succinate, maleate, gentisinate, fumarate, gluconate, glucuronate, saccharate, formate, benzoate, glutamate, methanesulfonate, ethanesulfonate, benzenesulfonate, p-toluenesulfonate and palmoate [i.e., 1,1'-
15 methylene-bis-(2-hydroxy-3-naphthoate)] salts. Although such salts must be pharmaceutically acceptable for administration to a subject, e.g., a mammal, it is often desirable in practice to initially isolate a tetracycline compound of the invention from the reaction mixture as a pharmaceutically unacceptable salt and then simply convert the latter back to the free base compound by treatment with an alkaline reagent and
20 subsequently convert the latter free base to a pharmaceutically acceptable acid addition salt. The acid addition salts of the base compounds of this invention are readily prepared by treating the base compound with a substantially equivalent amount of the chosen mineral or organic acid in an aqueous solvent medium or in a suitable organic solvent, such as methanol or ethanol. Upon careful evaporation of the solvent, the
25 desired solid salt is readily obtained. The preparation of other tetracycline compounds of the invention not specifically described in the foregoing experimental section can be accomplished using combinations of the reactions described above that will be apparent to those skilled in the art.

 The preparation of other tetracycline compounds of the invention not
30 specifically described in the foregoing experimental section can be accomplished using combinations of the reactions described above that will be apparent to those skilled in the art.

 The tetracycline compounds of the invention that are acidic in nature are capable of forming a wide variety of base salts. The chemical bases that may be used as
35 reagents to prepare pharmaceutically acceptable base salts of those tetracycline compounds of the invention that are acidic in nature are those that form non-toxic base salts with such compounds. Such non-toxic base salts include, but are not limited to

those derived from such pharmaceutically acceptable cations such as alkali metal cations (e.g., potassium and sodium) and alkaline earth metal cations (e.g., calcium and magnesium), ammonium or water-soluble amine addition salts such as N-methylglucamine-(meglumine), and the lower alkanolammonium and other base salts of pharmaceutically acceptable organic amines. The pharmaceutically acceptable base addition salts of tetracycline compounds of the invention that are acidic in nature may be formed with pharmaceutically acceptable cations by conventional methods. Thus, these salts may be readily prepared by treating the tetracycline compound of the invention with an aqueous solution of the desired pharmaceutically acceptable cation and evaporating the resulting solution to dryness, preferably under reduced pressure. Alternatively, a lower alkyl alcohol solution of the tetracycline compound of the invention may be mixed with an alkoxide of the desired metal and the solution subsequently evaporated to dryness.

The preparation of other tetracycline compounds of the invention not specifically described in the foregoing experimental section can be accomplished using combinations of the reactions described above that will be apparent to those skilled in the art.

The tetracycline compounds of the invention and pharmaceutically acceptable salts thereof can be administered via either the oral, parenteral or topical routes. In general, these compounds are most desirably administered in effective dosages, depending upon the weight and condition of the subject being treated and the particular route of administration chosen. Variations may occur depending upon the species of the subject being treated and its individual response to said medicament, as well as on the type of pharmaceutical formulation chosen and the time period and interval at which such administration is carried out.

The pharmaceutical compositions of the invention may be administered alone or in combination with other known compositions for treating tetracycline responsive states in a subject, e.g., a mammal. Preferred mammals include pets (e.g., cats, dogs, ferrets, etc.), farm animals (cows, sheep, pigs, horses, goats, etc.), lab animals (rats, mice, monkeys, etc.), and primates (chimpanzees, humans, gorillas). The language "in combination with" a known composition is intended to include simultaneous administration of the composition of the invention and the known composition, administration of the composition of the invention first, followed by the known composition and administration of the known composition first, followed by the composition of the invention. Any of the therapeutically composition known in the art for treating tetracycline responsive states can be used in the methods of the invention.

The tetracycline compounds of the invention may be administered alone or in combination with pharmaceutically acceptable carriers or diluents by any of the routes previously mentioned, and the administration may be carried out in single or multiple doses. For example, the novel therapeutic agents of this invention can be administered advantageously in a wide variety of different dosage forms, i.e., they may be combined with various pharmaceutically acceptable inert carriers in the form of tablets, capsules, lozenges, troches, hard candies, powders, sprays, creams, salves, suppositories, jellies, gels, pastes, lotions, ointments, aqueous suspensions, injectable solutions, elixirs, syrups, and the like. Such carriers include solid diluents or fillers, sterile aqueous media and various non-toxic organic solvents, etc. Moreover, oral pharmaceutical compositions can be suitably sweetened and/or flavored. In general, the therapeutically-effective compounds of this invention are present in such dosage forms at concentration levels ranging from about 5.0% to about 70% by weight.

For oral administration, tablets containing various excipients such as microcrystalline cellulose, sodium citrate, calcium carbonate, dicalcium phosphate and glycine may be employed along with various disintegrants such as starch (and preferably corn, potato or tapioca starch), alginic acid and certain complex silicates, together with granulation binders like polyvinylpyrrolidone, sucrose, gelatin and acacia. Additionally, lubricating agents such as magnesium stearate, sodium lauryl sulfate and talc are often very useful for tableting purposes. Solid compositions of a similar type may also be employed as fillers in gelatin capsules; preferred materials in this connection also include lactose or milk sugar as well as high molecular weight polyethylene glycols. When aqueous suspensions and/or elixirs are desired for oral administration, the active ingredient may be combined with various sweetening or flavoring agents, coloring matter or dyes, and, if so desired, emulsifying and/or suspending agents as well, together with such diluents as water, ethanol, propylene glycol, glycerin and various like combinations thereof.

For parenteral administration (including intraperitoneal, subcutaneous, intravenous, intradermal or intramuscular injection), solutions of a therapeutic compound of the present invention in either sesame or peanut oil or in aqueous propylene glycol may be employed. The aqueous solutions should be suitably buffered (preferably pH greater than 8) if necessary and the liquid diluent first rendered isotonic. These aqueous solutions are suitable for intravenous injection purposes. The oily solutions are suitable for intraarticular, intramuscular and subcutaneous injection purposes. The preparation of all these solutions under sterile conditions is readily accomplished by standard pharmaceutical techniques well known to those skilled in the art. For parenteral application, examples of suitable preparations include solutions,

preferably oily or aqueous solutions as well as suspensions, emulsions, or implants, including suppositories. Therapeutic compounds may be formulated in sterile form in multiple or single dose formats such as being dispersed in a fluid carrier such as sterile physiological saline or 5% saline dextrose solutions commonly used with injectables.

5 Additionally, it is also possible to administer the compounds of the present invention topically when treating inflammatory conditions of the skin. Examples of methods of topical administration include transdermal, buccal or sublingual application. For topical applications, therapeutic compounds can be suitably admixed in a pharmacologically inert topical carrier such as a gel, an ointment, a lotion or a cream.
10 Such topical carriers include water, glycerol, alcohol, propylene glycol, fatty alcohols, triglycerides, fatty acid esters, or mineral oils. Other possible topical carriers are liquid petrolatum, isopropylpalmitate, polyethylene glycol, ethanol 95%, polyoxyethylene monolaurate 5% in water, sodium lauryl sulfate 5% in water, and the like. In addition, materials such as anti-oxidants, humectants, viscosity stabilizers and the like also may
15 be added if desired.

For enteral application, particularly suitable are tablets, dragees or capsules having talc and/or carbohydrate carrier binder or the like, the carrier preferably being lactose and/or corn starch and/or potato starch. A syrup, elixir or the like can be used wherein a sweetened vehicle is employed. Sustained release compositions can be
20 formulated including those wherein the active component is protected with differentially degradable coatings, e.g., by microencapsulation, multiple coatings, etc.

In addition to treatment of human subjects, the therapeutic methods of the invention also will have significant veterinary applications, e.g. for treatment of livestock such as cattle, sheep, goats, cows, swine and the like; poultry such as chickens,
25 ducks, geese, turkeys and the like; horses; and pets such as dogs and cats. Also, the compounds of the invention may be used to treat non-animal subjects, such as plants.

It will be appreciated that the actual preferred amounts of active compounds used in a given therapy will vary according to the specific compound being utilized, the particular compositions formulated, the mode of application, the particular
30 site of administration, etc. Optimal administration rates for a given protocol of administration can be readily ascertained by those skilled in the art using conventional dosage determination tests conducted with regard to the foregoing guidelines.

In general, compounds of the invention for treatment can be administered to a subject in dosages used in prior tetracycline therapies. See, for example, the
35 *Physicians' Desk Reference*. For example, a suitable effective dose of one or more compounds of the invention will be in the range of from 0.01 to 100 milligrams per kilogram of body weight of recipient per day, preferably in the range of from 0.1 to 50

milligrams per kilogram body weight of recipient per day, more preferably in the range of 1 to 20 milligrams per kilogram body weight of recipient per day. The desired dose is suitably administered once daily, or several sub-doses, e.g. 2 to 5 sub-doses, are administered at appropriate intervals through the day, or other appropriate schedule.

- 5 It will also be understood that normal, conventionally known precautions will be taken regarding the administration of tetracyclines generally to ensure their efficacy under normal use circumstances. Especially when employed for therapeutic treatment of humans and animals *in vivo*, the practitioner should take all sensible precautions to avoid conventionally known contradictions and toxic effects. Thus, the conventionally
- 10 recognized adverse reactions of gastrointestinal distress and inflammations, the renal toxicity, hypersensitivity reactions, changes in blood, and impairment of absorption through aluminum, calcium, and magnesium ions should be duly considered in the conventional manner.

- Furthermore, the invention also pertains to the use of a tetracycline
- 15 compound of formula I, for the preparation of a medicament. The medicament may include a pharmaceutically acceptable carrier and the tetracycline compound is an effective amount, e.g., an effective amount to treat a tetracycline responsive state.

EXEMPLIFICATION OF THE INVENTION

- 20 Compounds of the invention may be made as described below, with modifications to the procedure below within the skill of those of ordinary skill in the art.

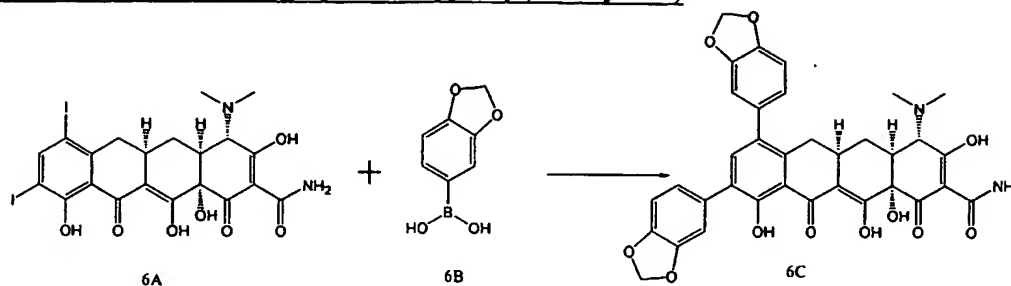
Example 1: Synthesis of Compounds of the Invention

25 7,9-Diiodosancycline

- 30 30.0 mL of concentrated sulfuric acid was added to 1.00g of sancycline hydrochloride hemihydrate with stirring and the solution cooled to 0°C. 1.09g of N-iodosuccinimide was added portionwise to the solution over one hr and the reaction mixture monitored by HPLC and TLC. The reaction mixture was poured into 250 mL of ice water, extracted three times with n-butanol, and the solvent removed under reduced pressure. The crude residue was purified by preparative HPLC yielding 787mg (61%) of 7-iodosancycline and 291mg (22%) of 7,9-diiodosancycline as yellow and dark yellow crystals respectively.

MS (FAB): m/z 667 (M+H)

- 35 ¹H NMR (Methanol d-4, 300MHz) δ 8.35 (s, 1H), 3.78 (s, 1H), 3.33 (s, 2H), 2.88 (s, 7H), 2.41 (m, 2H), 1.41 (m, 5H).

Compound HZ (7,9-Bis(3,4-Methylenedioxyphenyl)-Sancycline)

SCHEME 6

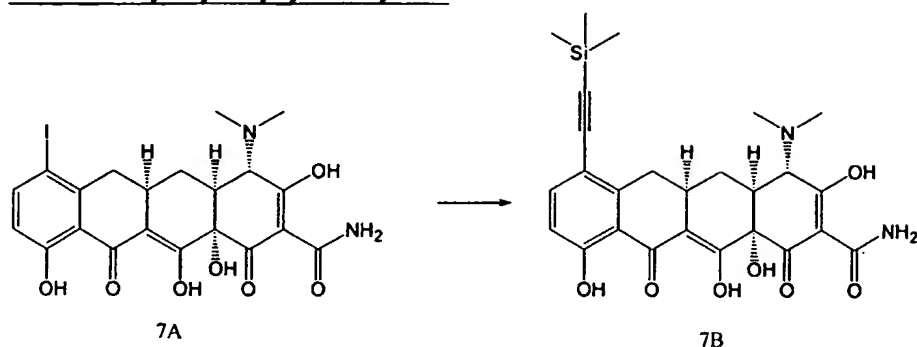
- 5 577 mg (0.74 mmol) 7,9-diiodo sancycline (6C) and 8.3 mg (0.37 mmol) palladium acetate were dissolved in 25 ml methanol, under a nitrogen atmosphere. The solution was warmed to 60 °C. After stirring for ten minutes 234 mg (2.22 mmol), sodium carbonate was added followed by 246 mg (1.48 mmol) of 3,4-methylenedioxyphenyl boronic acid (6B). The reaction was complete in 4 hours. The
- 10 reaction mixture was filtered through a celite bed and concentrated under reduced pressure. This crude product was purified by preparative liquid chromatography using a C₁₈ stationary phase with eluent A: 0.1% TFA in water and eluent B: 0.1% TFA in acetonitrile. 60 mg pure product was isolated (6C).

15 7 Iodo Sancycline

- One gram of sancycline was dissolved in 25 mL of TFA (trifluoroacetic acid) that was cooled to 0 °C (on ice). 1.2 equivalents of N-iodosuccinimide (NIS) was added to the reaction mixture and reacted for forty minutes. The reaction was removed from the ice bath and was allowed to react at room temperature for an additional five
- 20 hours. The mixture was then analyzed by HPLC and TLC, was driven to completion by the stepwise addition of NIS. After completion of the reaction, the TFA was removed *in vacuo* and 3 mL of MeOH was added to dissolve the residue. The methanolic solution was added slowly to a rapidly stirring solution of diethyl ether to form a greenish brown precipitate. The 7-iodo isomer of sancycline was purified by treating the 7-iodo
- 25 product with activated charcoal., filtering through Celite, and subsequent removal of the solvent *in vacuo* to produce the 7-isomer compound as a pure yellow solid in 75% yield. MS(M+H) (formic acid solvent) 541.3.

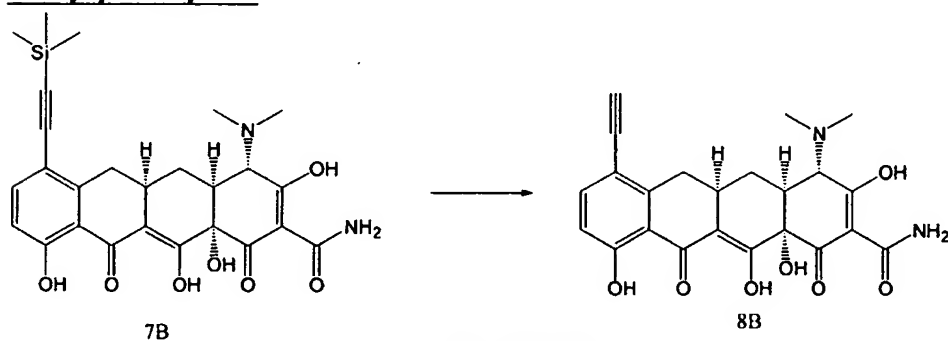
\Rt: Hypersil C18 BDS Column, 11.73

- ¹H NMR (Methanol d₄-300 MHz) δ 7.87-7.90 (d, 1H), 6.66-6.69 (d, 1H), 4.06 (s, 1H),
- 30 2.98 (s, 6H), 2.42 (m, 1H), 2.19 (m, 1H), 1.62 (m, 4H), 0.99 (m, 2H)

7-Tetramethylsilylethynyl-Sancycline

SCHEME 7

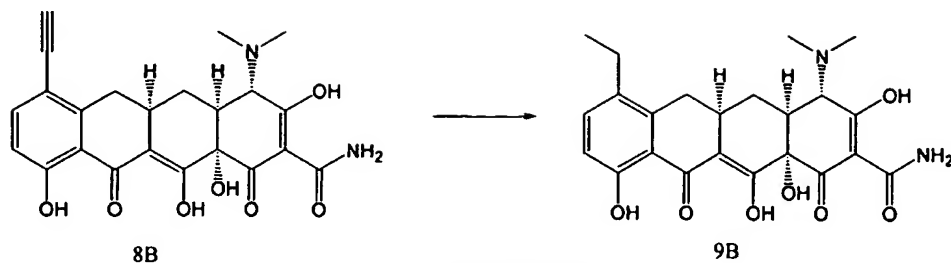
- 5 To a solution of 6.54 g (10 mmol) 7-iodo-sancycline trifluoroacetate 500 mg tetrakis-triphenylphosphino-palladate, 500 mg copper(I) iodide, 100 mg palladium acetate and 30 ml triethylamine 3 ml trimethylsilyl-acetylene was added. The reaction mixture was stirred at room temperature for two hours than filtered through a celite bed and concentrated. The dry material was picked up in methanol, the insolubles were
- 10 filtered out. The solution was concentrated to recover 6.8 g of the product (7B).

7-Ethynyl-Sancycline

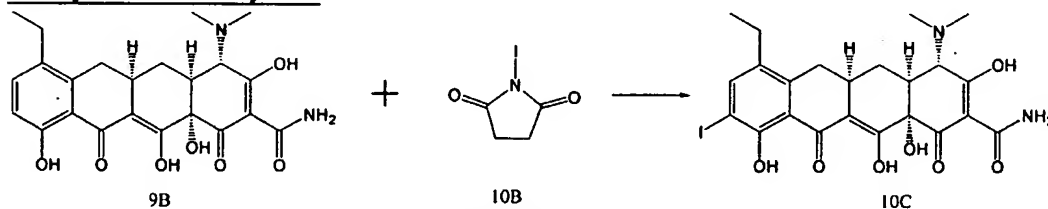
SCHEME 8

15

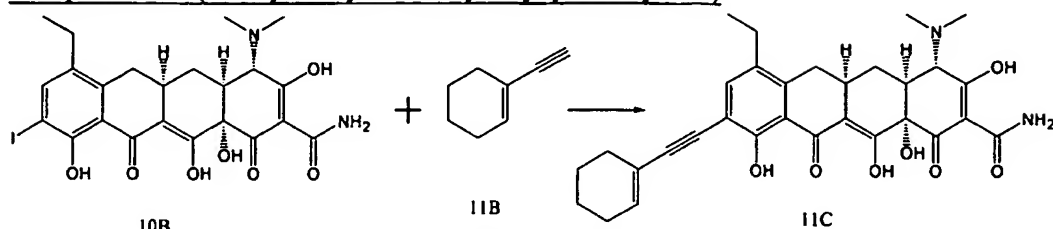
- 7-Tetramethylsilylethynyl-sancycline (7B) is dissolved in 300 ml methanol, and stirred at 40 °C with 6.8 g potassium carbonate. When no starting material could be detected by HPLC (~3 hours), the reaction mixture was cooled in an ice/water bath and solids were removed by filtration. The structure of the alkyne (8B) was confirmed by
- 20 LCMS. 8B was then used without further purification in the next step.

7-Ethyl-Sancycline**SCHEME 9**

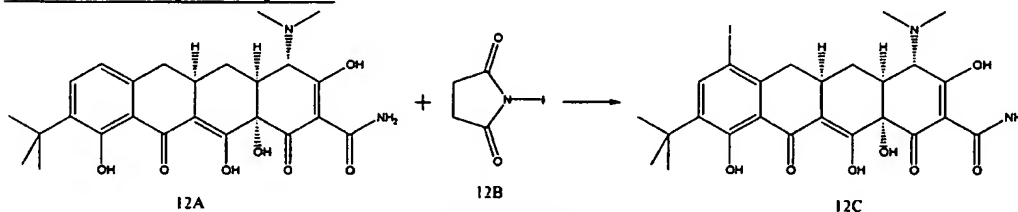
- 5 10% palladium catalyst on charcoal (1 g) was added to 7-ethynyl sancycline (8C) in a saturated methanol hydrochloric acid solvent. The mixture was placed in a hydrogenator under 50 psi hydrogen pressure. The reaction was completed in ~8 hours. The catalyst was filtered off, and the resulting solution was concentrated. The crude product was purified by preparative liquid chromatography using a C₁₈ stationary phase with eluent A: 0.1% TFA in water and eluent B: 0.1% TFA in acetonitrile. The combined clean fractions are concentrated and hydrochloric acid saturated isopropanol added. The pure product is precipitated by addition of diethylether and filtered off. After drying under reduced pressure 3.2 g of 7-ethyl-sancycline (9B) was isolated.

15 7-Ethyl-9-Iodo-Sancycline**SCHEME 10**

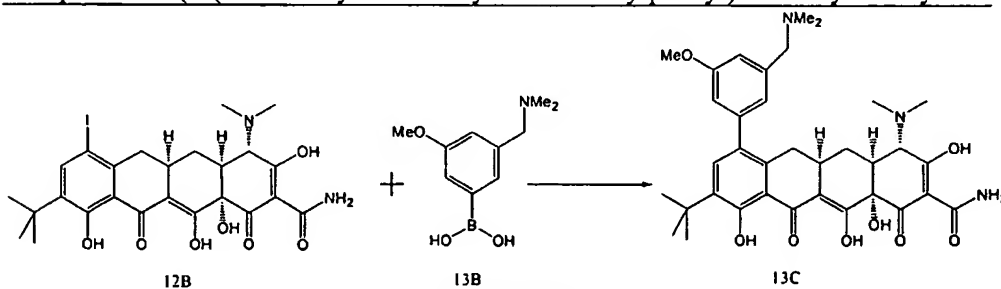
- 20 7-Ethyl-Sancycline (9B, 6.7 mmol, 3.2 g) was dissolved in 75 ml methanesulfonic acid at room temperature. N-iodo succinimide (10B, 13.5 mmol, 3.05 g) was added over two hours in 6 portions. After two hours diethyl ether was added, and the precipitate was filtered off and dried. The crude product was purified by preparative liquid chromatography using a C₁₈ stationary phase with eluent A: 0.1% TFA in water and eluent B: 0.1% TFA in acetonitrile. 1.5 g of pure product (10C) was isolated.
- 25

Compound HO (7-Ethyl-9-Cyclohexenylethynyl-Sancycline)**SCHEME 11**

- 5 To a solution of 7-ethyl-sancycline (500 mg, 1.13 mmol), 50 mg tetrakis-triphenylphosphino-palladate, 50 mg copper(I) iodide, 10 mg palladium acetate and 3 ml triethylamine 0.1 ml cyclohexenyl-acetylene was added. The reaction mixture was stirred at 60 °C for one hour, filtered through a celite bed and concentrated. The dry material was dissolved in methanol and filtered. The solution was then concentrated and
- 10 purified using preparative liquid chromatography. The preparative liquid chromatography used a C₁₈ stationary phase with eluent A: 0.1% TFA in water and eluent B: 0.1% TFA in acetonitrile. 100 mg of Compound HO was isolated.

7-iodo-9-t-Butyl-Sancycline**SCHEME 12**

- 9-t-butyl-sancycline (12A, 1.13 g, 2 mmol) was dissolved in 5 ml methanesulfonic acid (0.448, 2 mmol). N-iodosuccinimide (12B) was added at room temperature over one hour in four portions. The product (12C) was precipitated with diethyl ether, filtered off and used in other reaction without further purification.

Compound ID (7-(2-Methoxy-5-Dimethylaminomethylphenyl)-9-t-Butyl-Sancycline)**SCHEME 13**

7-Iodo-9-t-butyl-sancycline (12B, 710 mg, 1.0 mmol) and palladium acetate (22.4 mg, 0.1 mmol) were dissolved in 25 ml of methanol under a nitrogen atmosphere. Cesium carbonate (3.25 g, 10 mmol) and 2-methoxy-5-dimethylaminomethylphenylboronic acid (13B, 0.435 g, 0.15 mmol) were added. The reaction mixture was stirred at 5 60 °C for two hours and then filtered through a celite bed and concentrated under reduced pressure. The crude product was purified by preparative liquid chromatography using a C₁₈ stationary phase with eluent A: 0.1% TFA in water and eluent B: 0.1% TFA in acetonitrile. 210 mg of Compound ID (13C) was isolated.

10 Example 2: *In vitro* Minimum Inhibitory Concentration (MIC) Assay

The following assay is used to determine the efficacy of minocycline compounds against common bacteria. 2 mg of each compound is dissolved in 100 µl of DMSO. The solution is then added to cation-adjusted Mueller Hinton broth (CAMHB), which results in a final compound concentration of 200 µg per ml. The minocycline 15 compound solutions are diluted to 50 µL volumes, with a test compound concentration of .098 µg/ml. Optical density (OD) determinations are made from fresh log-phase broth cultures of the test strains. Dilutions are made to achieve a final cell density of 1x10⁶ CFU/ml. At OD=1, cell densities for different genera should be approximately:

20	<i>E. coli</i>	1x10 ⁹ CFU/ml
	<i>S. aureus</i>	5x10 ⁸ CFU/ml
	<i>Enterococcus sp.</i>	2.5x10 ⁹ CFU/ml

50 µl of the cell suspensions are added to each well of microtiter plates. 25 The final cell density should be approximately 5x10⁵ CFU/ml. These plates are incubated at 35°C in an ambient air incubator for approximately 18 hr. The plates are read with a microplate reader and are visually inspected when necessary. The MIC is defined as the lowest concentration of the minocycline compound that inhibits growth. Compounds of the invention indicate good inhibition of growth.

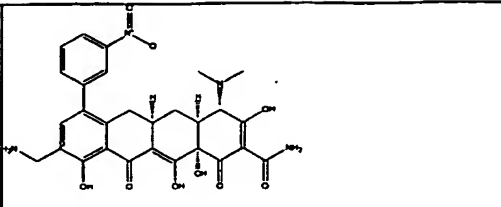
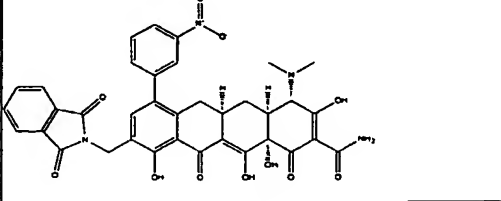
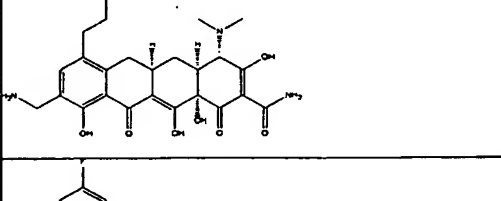
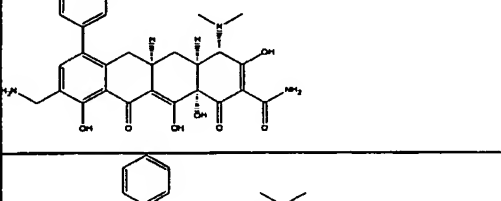
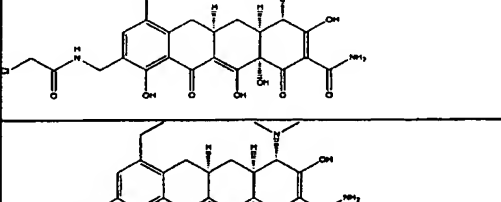
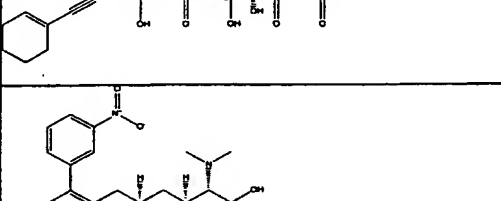
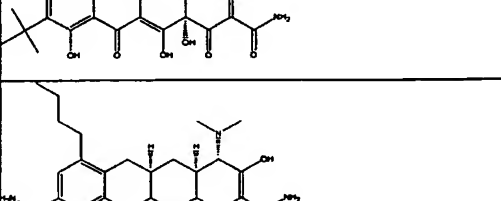
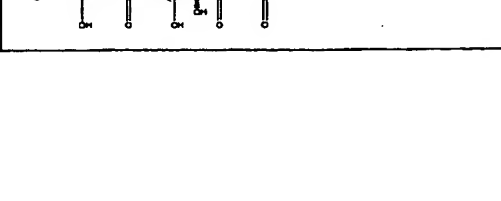
30 In Table 2, compounds which were good inhibitors of growth of a particular bacteria are indicated with *, compounds which were very good inhibitors of a particular bacteria are indicated with **, and compounds which were particularly good inhibitors of a particular bacteria are indicated with ***.

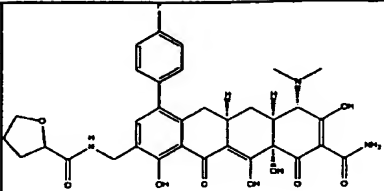
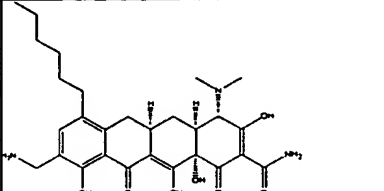
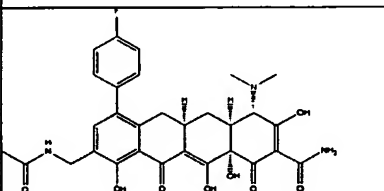
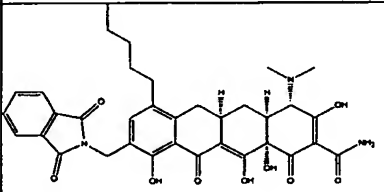
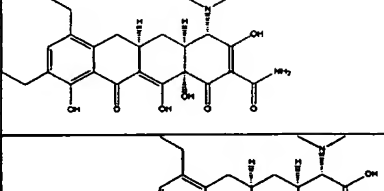
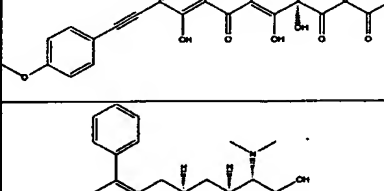
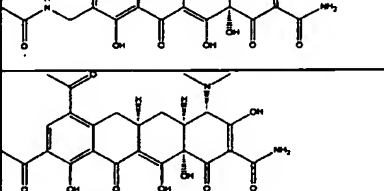
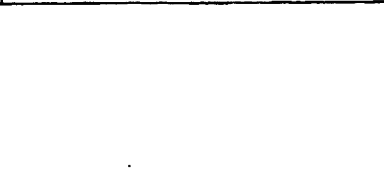
EQUIVALENTS

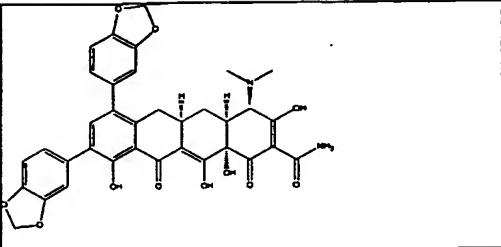
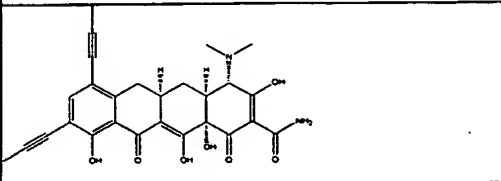
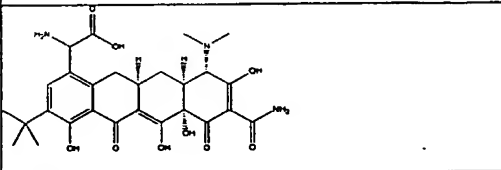
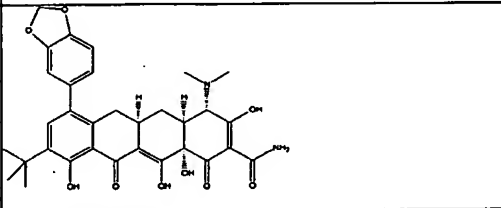
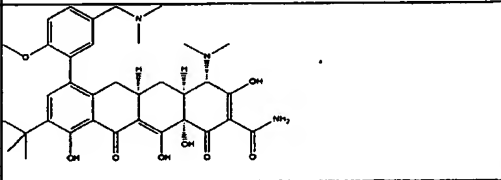
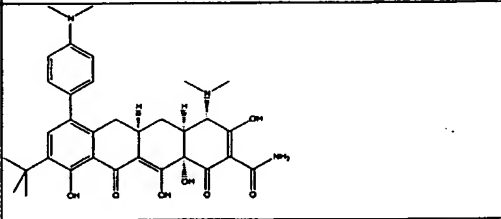
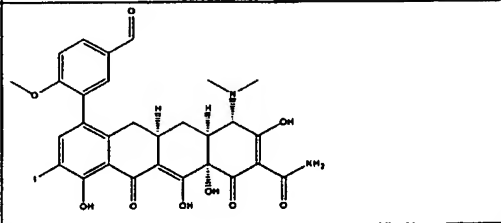
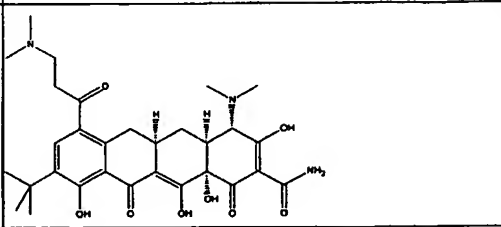
Those skilled in the art will recognize, or be able to ascertain using no more than routine experimentation, numerous equivalents to the specific procedures described herein. Such equivalents are considered to be within the scope of the present invention and are covered by the following claims. The contents of all references, issued patents, and published patent applications cited throughout this application are hereby incorporated by reference. The appropriate components, processes, and methods of those patents, applications and other documents may be selected for the present invention and embodiments thereof.

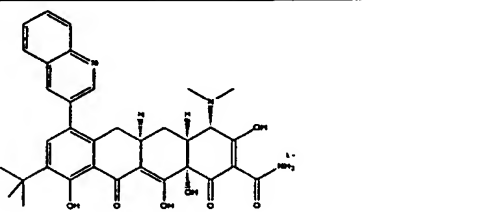
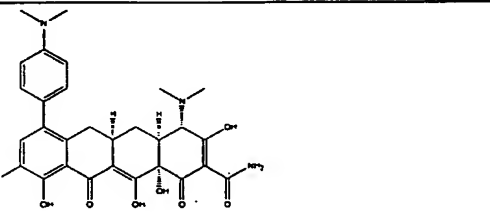
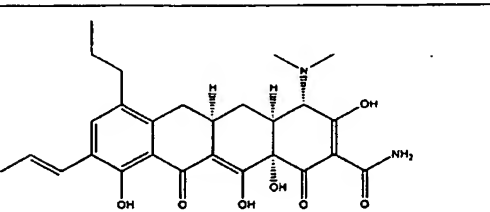
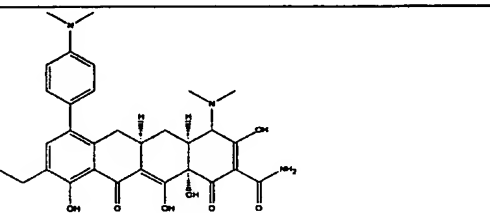
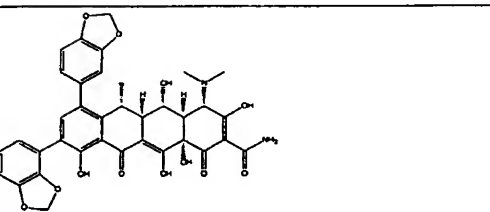
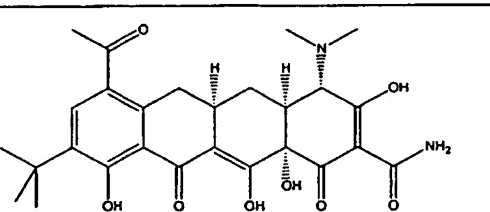
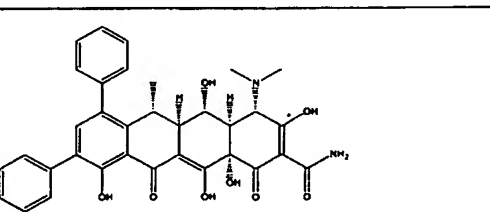
TABLE 2

ID	STRUCTURE	<i>S. aureus</i>	<i>E. hirae</i>	<i>E. coli</i>
HA		NT	NT	NT
HB		**	**	*
HC		*	*	*
HD		NT	NT	NT
HE		**	**	*
HF		*	**	*
HG		**	*	*
HI		**	**	*

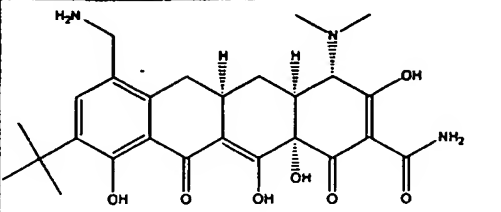
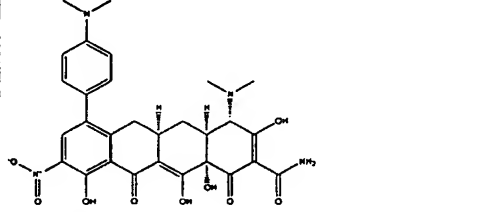
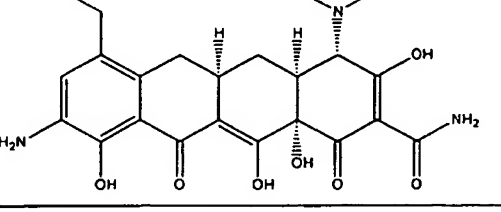
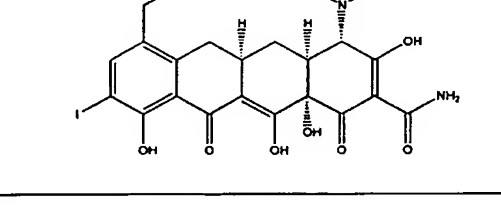
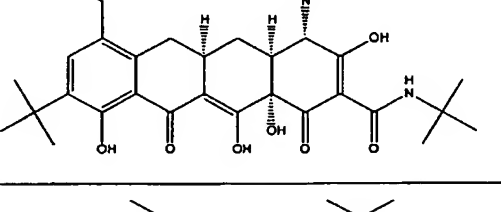
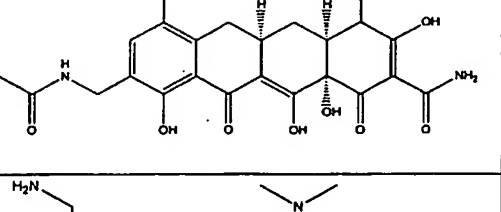
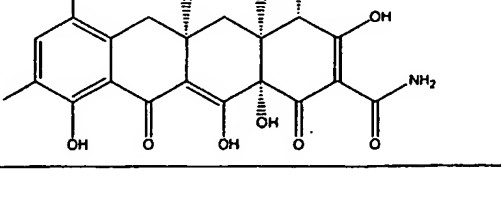
HJ		**	**	*
HK		**	**	*
HL		**	**	**
HM		**	**	**
HN		***	**	*
HO		***	***	*
HP		**	***	*
HQ		**	**	**

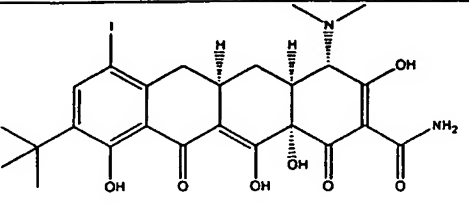
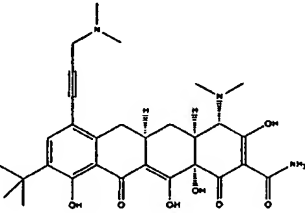
HR		**	**	*
HS		**	***	***
HT		**	**	*
HU		**	***	*
HV		***	***	**
HW		**	**	*
HX		**	***	*
HY		NT	NT	NT

HZ		***	**	*
IA		*	*	*
IB		NT	NT	NT
IC		NT	NT	NT
ID		NT	NT	NT
IE		NT	NT	NT
IF		NT	NT	NT
IG		NT	NT	NT

IH		NT	NT	NT
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IN		NT	NT	NT

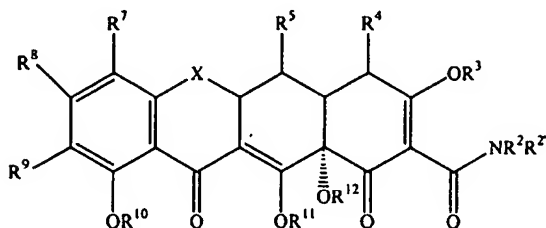
IO		NT	NT	NT
IP		NT	NT	NT
IQ		NT	NT	NT
IR		NT	NT	NT
IS		NT	NT	NT
IT		NT	NT	NT
IU		NT	NT	NT

IV		NT	NT	NT
IW		NT	NT	NT
IX		NT	NT	NT
IY		NT	NT	NT
IZ		NT	NT	NT
JA		NT	NT	NT
JB		NT	NT	NT

JC		NT	NT	NT
JD		NT	NT	NT

CLAIMS

1. A 7, 9-substituted tetracycline compound of Formula I:



(I)

wherein:

- X is $\text{CHC}(\text{R}^{13}\text{Y}'\text{Y})$, $\text{CR}^{6'}\text{R}^6$, S, NR^6 , or O;
 R^2 , $\text{R}^{2'}$, $\text{R}^{4'}$, and $\text{R}^{4''}$ are each independently hydrogen, alkyl, alkenyl, alkynyl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, arylalkyl, aryl, heterocyclic, heteroaromatic or a prodrug moiety;
 R^4 is $\text{NR}^{4'}\text{R}^{4''}$, alkyl, alkenyl, alkynyl, hydroxyl, halogen, or hydrogen;
 $\text{R}^{2'}$, R^3 , R^{10} , R^{11} and R^{12} are each hydrogen or a pro-drug moiety;
 R^5 is hydroxyl, hydrogen, thiol, alkanoyl, aroyl, alkaroyl, aryl, heteroaromatic, alkyl, alkenyl, alkynyl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, arylalkyl, alkyl carbonyloxy, or aryl carbonyloxy;
 R^6 and $\text{R}^{6'}$ are each independently hydrogen, methylene, absent, hydroxyl, halogen, thiol, alkyl, alkenyl, alkynyl, aryl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, or an arylalkyl;
 R^7 is nitro, alkyl, alkenyl, alkynyl, aryl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, arylalkyl, amino, arylalkenyl, arylalkynyl, or $-(\text{CH}_2)_{0-3}\text{NR}^{7c}\text{C}(=\text{W}')\text{WR}^{7a}$;
 R^9 is nitro, alkyl, alkenyl, alkynyl, aryl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, arylalkyl, amino, arylalkenyl, arylalkynyl, thionitroso, or $-(\text{CH}_2)_{0-3}\text{NR}^{9c}\text{C}(=\text{Z}')\text{ZR}^{9a}$;
Z is $\text{CR}^{9d}\text{R}^{9e}$, S, NR^{9b} or O;
Z' is O, S, or NR^{9f} ;
W is $\text{CR}^{7d}\text{R}^{7e}$, S, NR^{7b} or O;
W' is O, NR^{7f} S;
 R^{7a} , R^{7b} , R^{7c} , R^{7d} , R^{7e} , R^{9a} , R^{9b} , R^{9c} , R^{9d} , and R^{9e} are each independently hydrogen, acyl, alkyl, alkenyl, alkynyl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, arylalkyl, aryl, heterocyclic, heteroaromatic or a prodrug moiety;
 R^8 is hydrogen, hydroxyl, halogen, thiol, alkyl, alkenyl, alkynyl, aryl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, or an arylalkyl;

R^{13} is hydrogen, hydroxy, alkyl, alkenyl, alkynyl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, or an arylalkyl; and

Y' and Y are each independently hydrogen, halogen, hydroxyl, cyano, sulfhydryl, amino, alkyl, alkenyl, alkynyl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, or an arylalkyl, and pharmaceutically acceptable salts thereof, provided that R^7 and R^9 are not both unsubstituted phenyl.

2. The tetracycline compound of claim 1, wherein X is CR^6R^6' ; R^2 , $R^{2'}$, R^6 , $R^{6'}$, R^8 , R^{10} , R^{11} , and R^{12} are each hydrogen; R^4 is $NR^{4'}R^{4''}$; $R^{4'}$ and $R^{4''}$ are lower alkyl; and R^5 is hydroxy or hydrogen.

3. The tetracycline compound of claim 2, wherein $R^{4'}$ and $R^{4''}$ are each methyl and R^5 is hydrogen.

4. The tetracycline compound of any one of claims 1-3, wherein R^7 is aryl.

5. The tetracycline compound of claim 4, wherein R^7 is substituted or unsubstituted phenyl.

6. The tetracycline compound of claim 5, wherein said phenyl is substituted with one or more substituents selected from the group consisting of alkyl, alkenyl, halogen, hydroxyl, alkoxy, alkylcarbonyloxy, alkyloxycarbonyl, arylcarbonyloxy, alkoxycarbonylamino, alkoxycarbonyloxy, aryloxycarbonyloxy, carboxylate, alkylcarbonyl, alkylaminoacarbonyl, arylalkyl aminocarbonyl, alkenylaminocarbonyl, alkylcarbonyl, arylcarbonyl, aminoalkyl, arylalkylcarbonyl, alkenylcarbonyl, alkoxycarbonyl, silyl, aminocarbonyl, alkylthiocarbonyl, phosphate, aralkyl, phosphonato, phosphinato, cyano, amino, acylamino, amido, imino, sulfhydryl, alkylthio, sulfate, arylthio, thiocarboxylate, alkylsulfinyl, sulfonato, sulfamoyl, sulfonamido, nitro, cyano, azido, heterocyclyl, alkylaryl, aryl and heteroaryl.

7. The tetracycline compound of claim 6, wherein said substituent is substituted or unsubstituted alkyl, nitro, halogen, amino, or alkoxy.

8. The tetracycline compound of claim 7, wherein said halogen substituent is fluorine.

9. The tetracycline compound of claim 7, wherein said alkoxy substituent is methylenedioxy or methoxy.
10. The tetracycline compound of claim 6, wherein said amino substituent is
5 dialkylamino.
11. The tetracycline compound of claim 5, wherein R⁷ is unsubstituted phenyl.
- 10 12. The tetracycline compound of any one of claims 1-3, wherein R⁷ is substituted or unsubstituted alkyl.
13. The tetracycline compound of claim 12, wherein said alkyl is unsubstituted alkyl.
- 15 14. The tetracycline compound of claim 13, wherein said alkyl is methyl, ethyl, propyl, butyl, pentyl, or hexyl.
15. The tetracycline compound of claim 12, wherein said alkyl comprises a
20 ring.
16. The tetracycline compound of claim 15, wherein said ring is cyclohexyl.
17. The tetracycline compound of claim 12, wherein said alkyl is substituted
25 with one or more substituents selected from the group consisting of alkenyl, halogen, hydroxyl, alkoxy, alkylcarbonyloxy, alkyloxycarbonyl, arylcarbonyloxy, arylcarbonylamino, alkoxycarbonylamino, alkoxycarbonyloxy, aryloxycarbonyloxy, carboxylate, alkylcarbonyl, alkylaminoacarbonyl, arylalkyl aminocarbonyl, alkenylaminocarbonyl, alkylcarbonyl, arylcarbonyl, aminoalkyl, arylalkylcarbonyl,
30 alkenylcarbonyl, alkoxycarbonyl, silyl, aminocarbonyl, alkylthiocarbonyl, phosphate, aralkyl, phosphonato, phosphinato, cyano, amino, acylamino, amido, imino, sulfhydryl, alkylthio, sulfate, arylthio, thiocarboxylate, alkylsulfinyl, sulfonato, sulfamoyl, sulfonamido, nitro, cyano, azido, heterocyclyl, alkylaryl, aryl and heteroaryl.
- 35 18. The tetracycline compound of claim 17, wherein said heterocyclic substituent is isoindole-[1,3]-dione.

19. The tetracycline compound of claim 17, wherein said substituent is arylcarbonylamino.
20. The tetracycline compound of claim 19, wherein said aryl carbonyl
5 amino group is heteroaryl carbonyl amino.
21. The tetracycline compound of claim 18, wherein said substituent is amino or carboxylate.
- 10 22. The tetracycline compound of any one of claims 1-3, wherein said R⁷ is acyl.
23. The tetracycline compound of claim 22, wherein said acyl is acetyl.
- 15 24. The tetracycline compound of any one of claims 1-3, wherein R⁷ is substituted or unsubstituted alkynyl.
25. The tetracycline compound of claim 24, wherein R⁷ is substituted with one or more substituents selected from the group consisting of alkyl, alkenyl, halogen,
20 hydroxyl, alkoxy, alkylcarbonyloxy, alkylloxycarbonyl, arylcarbonyloxy, arylcarbonylamino, alkoxycarbonylamino, alkoxycarbonyloxy, aryloxycarbonyloxy, carboxylate, alkylcarbonyl, alkylaminoacarbonyl, arylalkyl aminocarbonyl, alkenylaminocarbonyl, alkylcarbonyl, arylcarbonyl, aminoalkyl, arylalkylcarbonyl, alkenylcarbonyl, alkoxycarbonyl, silyl, aminocarbonyl, alkylthiocarbonyl, phosphate,
25 aralkyl, phosphonato, phosphinato, cyano, amino, acylamino, amido, imino, sulfhydryl, alkylthio, sulfate, arylthio, thiocarboxylate, alkylsulfinyl, sulfonato, sulfamoyl, sulfonamido, nitro, cyano, azido, heterocyclyl, alkylaryl, aryl and heteroaryl.
26. The tetracycline compound of claim 25, wherein said alkyl substituent is
30 methyl.
27. The tetracycline compound of claim 25, wherein said aryl substituent is substituted or unsubstituted phenyl.
- 35 28. The tetracycline compound of claim 27, wherein said substituted phenyl is substituted with alkoxy.

29. The tetracycline compound of any one of claims 1-28, wherein R⁹ is substituted or unsubstituted aryl.
30. The tetracycline compound of claim 29, wherein R⁹ is substituted or
5 unsubstituted phenyl.
31. The tetracycline compound of claim 30, wherein said phenyl is substituted with one or more substituents selected from the group consisting of alkyl, alkenyl, halogen, hydroxyl, alkoxy, alkylcarbonyloxy, alkyloxycarbonyl, arylcarbonyloxy, alkoxycarbonylamino, alkoxycarbonyloxy, aryloxycarbonyloxy, carboxylate, alkylcarbonyl, alkylaminoacarbonyl, arylalkyl aminocarbonyl, alkenylaminocarbonyl, alkylcarbonyl, arylcarbonyl, aminoalkyl, arylalkylcarbonyl, alkenylcarbonyl, alkoxycarbonyl, silyl, aminocarbonyl, alkylthiocarbonyl, phosphate, aralkyl, phosphonato, phosphinato, cyano, amino, acylamino, amido, imino, sulfhydryl, alkylthio, sulfate, arylthio, thiocarboxylate, alkylsulfinyl, sulfonato, sulfamoyl, sulfonamido, nitro, cyano, azido, heterocyclyl, alkylaryl, aryl and heteroaryl.
32. The tetracycline compound of claim 31, wherein said substituent is substituted or unsubstituted alkyl, nitro, halogen, amino, or alkoxy.
- 20 33. The tetracycline compound of claim 32, wherein said alkoxy substituent is methylenedioxy.
34. The tetracycline compound of claim 30, wherein R⁹ is unsubstituted
25 phenyl.
35. The tetracycline compound of any one of claims 1-28, wherein R⁹ is substituted or unsubstituted alkyl.
- 30 36. The tetracycline compound of claim 12, wherein said alkyl is unsubstituted alkyl.
37. The tetracycline compound of claim 13, wherein said alkyl is methyl, ethyl, i-propyl, n-propyl, i-butyl, t-butyl, n-butyl, pentyl, or hexyl.
- 35 38. The tetracycline compound of claim 35, wherein said alkyl is substituted with one or more substituents selected from the group consisting of alkenyl, halogen,

hydroxyl, alkoxy, alkylcarbonyloxy, alkyloxycarbonyl, arylcarbonyloxy, arylcarbonylamino, alkoxycarbonylamino, alkoxycarbonyloxy, aryloxycarbonyloxy, alkylcarbonylamino, carboxylate, alkylcarbonyl, alkylaminoacarbonyl, arylalkyl aminocarbonyl, alkenylaminocarbonyl, alkylcarbonyl, arylcarbonyl, aminoalkyl, 5 arylalkylcarbonyl, alkenylcarbonyl, alkoxycarbonyl, silyl, aminocarbonyl, alkylthiocarbonyl, phosphate, aralkyl, phosphonato, phosphinato, cyano, amino, acylamino, amido, imino, sulfhydryl, alkylthio, sulfate, arylthio, thiocarboxylate, alkylsulfinyl, sulfonato, sulfamoyl, sulfonamido, nitro, cyano, azido, heterocyclyl, alkylaryl, aryl and heteroaryl.

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39. The tetracycline compound of claim 38, wherein said substituent is unsubstituted amino.

40. The tetracycline compound of claim 39, wherein said substituent is 15 arylcarbonylamino or alkylcarbonylamino.

41. The tetracycline compound of claim 40, wherein said aryl carbonyl amino group is heteroaryl carbonyl amino.

20 42. The tetracycline compound of claim 38, wherein said heterocyclic substituent is isoindole-[1,3]-dione.

43. The tetracycline compound of any one of claims 1-28, wherein said R⁹ is acyl.

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44. The tetracycline compound of claim 43, wherein said acyl is acetyl.

45. The tetracycline compound of any one of claims 1-28, wherein R⁹ is substituted or unsubstituted alkynyl.

30

46. The tetracycline compound of claim 45, wherein R⁹ is substituted with one or more substituents selected from the group consisting of alkyl, alkenyl, halogen, hydroxyl, alkoxy, alkylcarbonyloxy, alkyloxycarbonyl, arylcarbonyloxy, arylcarbonylamino, alkoxycarbonylamino, alkoxycarbonyloxy, aryloxycarbonyloxy, 35 carboxylate, alkylcarbonyl, alkylaminoacarbonyl, arylalkyl aminocarbonyl, alkenylaminocarbonyl, alkylcarbonyl, arylcarbonyl, aminoalkyl, arylalkylcarbonyl, alkenylcarbonyl, alkoxycarbonyl, silyl, aminocarbonyl, alkylthiocarbonyl, phosphate,

aralkyl, phosphonato, phosphinato, cyano, amino, acylamino, amido, imino, sulfhydryl, alkylthio, sulfate, arylthio, thiocarboxylate, alkylsulfinyl, sulfonato, sulfamoyl, sulfonamido, nitro, cyano, azido, heterocyclyl, alkylaryl, aryl and heteroaryl.

5 47. The tetracycline compound of claim 46, wherein said alkyl substituent is methyl.

48. The tetracycline compound of claim 46, wherein said aryl substituent is substituted or unsubstituted phenyl.

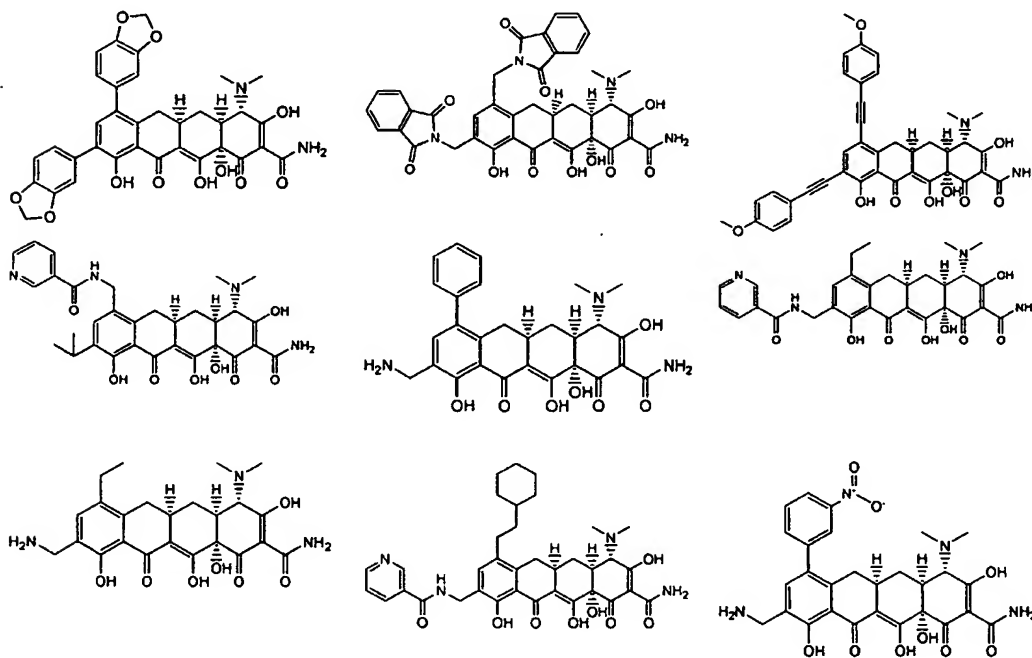
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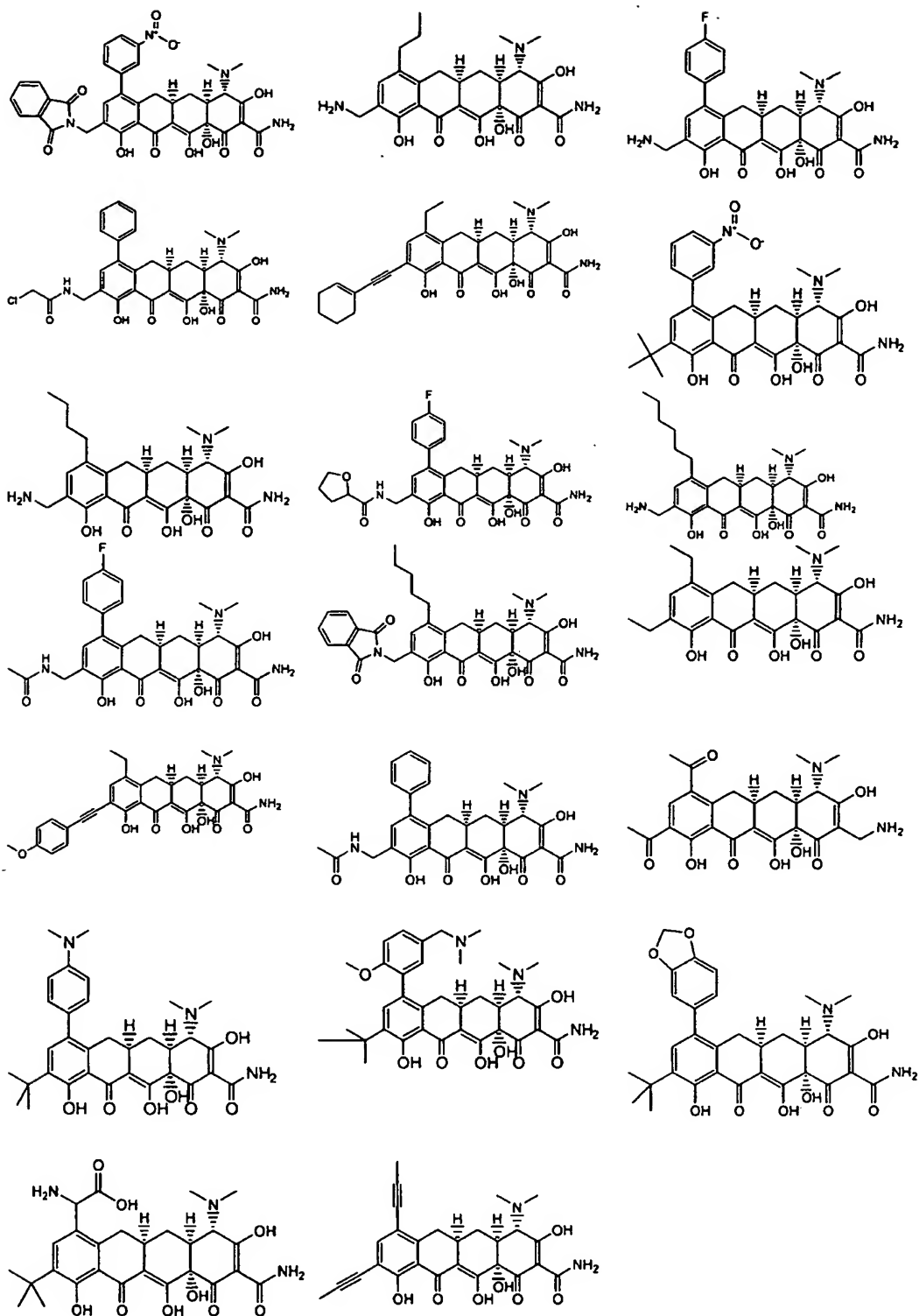
49. The tetracycline compound of claim 48, wherein said substituted phenyl is substituted with alkoxy.

50. The tetracycline compound of claim 46, wherein said substituent is

15 alkenyl.

51. A tetracycline compound selected from the group consisting of:





52. A method for treating a tetracycline responsive state in a subject, comprising administering to said subject a tetracycline compound of anyone of claims 1-51, such that the tetracycline responsive state is treated.
- 5 53. The method of claim 52, wherein said tetracycline responsive state is a bacterial infection.
54. The method of claim 53, wherein said bacterial infection is associated with *E. coli*.
- 10 55. The method of claim 53, wherein said bacterial infection is associated with *S. aureus*.
56. The method of claim 53, wherein said bacterial infection is associated with *E. faecalis*.
- 15 57. The method of claim 53, wherein said bacterial infection is resistant to other tetracycline antibiotics.
- 20 58. The method of claim 52, wherein said tetracycline compound is administered with a pharmaceutically acceptable carrier.
59. The method of claim 52, wherein said subject is a human.
- 25 60. A tetracycline compound selected from the group listed in Table 2.
61. A pharmaceutical composition comprising a therapeutically effective amount of a tetracycline compound of anyone of claims 1-51 or 60, and a pharmaceutically acceptable carrier.

INTERNATIONAL SEARCH REPORT

In ☐ national Application No

PCT/US 01/20722

A. CLASSIFICATION OF SUBJECT MATTER
 IPC 7 C07C237/26 A61K31/65

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07C A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DE 25 27 568 A (FARMACEUTICI ITALIA) 15 January 1976 (1976-01-15) claims 4,5,10,11,14,17-19; examples 2,5-7 ---	1-3,12, 17, 35-38,61
X	DE 23 46 535 A (FARMACEUTICI ITALIA) 11 April 1974 (1974-04-11) claims 1,5,7,13,15,17,19-22; examples 3-5,13,14,16,18,20-24,26 ---	1-3,13, 17, 35-37,61
X	WO 00 28983 A (ASHLEY ROBERT A ;HLAVKA JOSEPH J (US); COLLAGENEX PHARM INC (US)) 25 May 2000 (2000-05-25) claims 1-4 --- -/--	1-3,61

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

A document defining the general state of the art which is not considered to be of particular relevance

E earlier document but published on or after the International filing date

L document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

O document referring to an oral disclosure, use, exhibition or other means

P document published prior to the International filing date but later than the priority date claimed

T later document published after the International filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

X document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

Y document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

Z document member of the same patent family

Date of the actual completion of the international search

3 January 2002

Date of mailing of the international search report

10/01/2002

Name and mailing address of the ISA

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Rufet, J

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 01/20722

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 3 338 963 A (HOWARD BOOTHE JAMES ET AL) 29 August 1967 (1967-08-29) claims 1,10; examples 13,24,37,38 ----	1-3,61
X	US 3 433 834 A (WINTERBOTTOM ROBERT ET AL) 18 March 1969 (1969-03-18) column 3, paragraph 1; claim 1 -----	1-3,61

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 1-50,60,61 partly

Present claims 1-50, 60, 61 relate to an extremely large number of possible compounds/compositions. Support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of the compounds/compositions claimed. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Consequently, the search has been carried out for those parts of the claims which appear to be supported and disclosed, namely those parts relating to the compounds according to formula (I) of claim 1 wherein:

X = CH₂
 R₂ = R₂' = hydrogen
 R₄ = N(CH₃)₂
 R₅ = H, OH
 R₃ = R₁₀ = R₁₁ = R₁₂ = H
 R₈ = * (free site)

R₇ = nitro; amino; alkyl or alkoxy up to 6 carbon atoms; alkenyl or alkynyl up to 12 carbon atoms (C); -(CH₂)_n-N(**) with n = 1-3; -S(4*)-CH₂*; substituted or unsubstituted aryl, arylalkyl, arylalkenyl or arylalkynyl up to 15 carbon atoms

R₉ = nitro; amino; alkyl or alkoxy up to 6 C; alkenyl or alkynyl up to 12 C; -(CH₂)_n-N(2*) with n = 1-3; -S(4*)-CH₂*; substituted or unsubstituted aryl, arylalkyl, arylalkenyl, arylalkynyl up to 15 C; thionitroso

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Int. Patent Application No

PCT/US 01/20722

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
DE 2527568	A	15-01-1976	DE 2527568 A1	15-01-1976
			FR 2279720 A1	20-02-1976
			GB 1469384 A	06-04-1977
			JP 51019757 A	17-02-1976
DE 2346535	A	11-04-1974	AT 328613 B	25-03-1976
			AT 799673 A	15-06-1975
			AU 6033373 A	20-03-1975
			BE 804913 A1	18-03-1974
			CA 999855 A1	16-11-1976
			DE 2346535 A1	11-04-1974
			ES 418809 A1	16-03-1976
			FR 2208885 A1	28-06-1974
			GB 1413347 A	12-11-1975
			HU 167850 B	25-12-1975
			IE 38820 B1	07-06-1978
			JP 1151371 C	14-06-1983
			JP 49069653 A	05-07-1974
			JP 57041458 B	03-09-1982
			NL 7312648 A , B	20-03-1974
			SU 574145 A3	25-09-1977
			US 3901942 A	26-08-1975
			ZA 7307317 A	25-09-1974
WO 0028983	A	25-05-2000	AU 2345600 A	05-06-2000
			EP 1137410 A1	04-10-2001
			WO 0187823 A1	22-11-2001
			WO 0028983 A1	25-05-2000
US 3338963	A	29-08-1967	NONE	
US 3433834	A	18-03-1969	NONE	